Commercial Technology Transfer Optimization for Drug Substance Process Development

by
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Submitted to the MIT Sloan School of Management and the Department of Electrical Engineering & Computer Science in partial fulfillment of the requirements for the degree of

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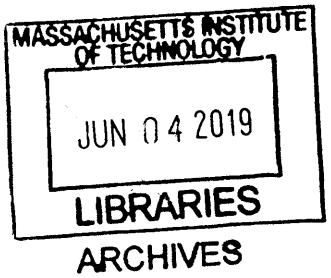

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ABSTRACT

Commercial technology transfer for biopharmaceuticals is the process of transferring process and product knowledge between process development and manufacturing organizations to achieve product realization. This process often occurs before phase 3 of clinical trials, where speed and agility are critical for preventing delays in clinical programs and ensuring commercial site readiness ahead of regulatory approval. As the market is evolving with new modalities and subsequent operational challenges, there is a heightened need to optimize the technology transfer process to sustain growth of products entering an organization's pipeline.

This graduate research project seeks to understand the business process workflow of commercial tech transfer and characterize its dynamics using discrete event simulation. Through this quantitative technique of business process modeling, knowledge regarding process bottlenecks and system constraints were revealed, leading to the identification of operational efficiencies which suggest a potential 19.5% reduction in lead times and 31.3% increase in organizational capacity. Furthermore, this work provides a platform for predicting program timelines and resource needs based on preliminary transfer requirements. These predictions can be updated in a Bayesian fashion for real-time project scheduling and capacity planning.

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I would like to give a special thank you to my family for fostering my passion in engineering and life sciences since I was young. Their unconditional love and support allowed me to pursue my interests, undertake new challenges, and push myself to new heights.

Finally, I thank MIT LGO for the countless memories shared. I could not have asked for a more humble, inspiring, and encouraging group of individuals to embark on this journey with. The lessons learned from my fellow classmates have been invaluable, and I look forward to witnessing the positive changes they make in this world in the chapters that lie ahead.

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Chapter 1 Introduction

1.1 Project Objective and Thesis Overview

The objective of this graduate research is to identify and evaluate a business strategy for commercial technology transfer optimization for Amgen's Drug Substance Process Development organization. The analysis and recommendations are supported by results from the characterization and modeling of commercial technology transfer using discrete event simulation. The model depicts the generation, transformation, and delivery of essential information through a systematic sequence of business process events, taking into consideration required resource and time distributions for each process activity. From this model, valuable insights on capacity and resource constraints were obtained, which were used during assessment of process improvement opportunities.

This thesis summarizes the research conducted on commercial technology transfer optimization for Drug Substance Process Development. To convey the objectives highlighted above, the document is divided into six sections.

Chapter 1 provides an overview of the project and contextual information on technology transfer in the biopharmaceutical industry, as well as introduces the research methodology and framework established.

Chapter 2 provides background information on the biopharmaceutical industry, including drug discovery and drug development processes. In addition, Chapter 2 reviews literature pertaining to the use of Lean applications and simulation modeling in biomanufacturing and commercial technology transfer.

Chapter 3 details the research methodology used in this work, including software tools and data collection techniques. Chapter 3 discusses the model used in the simulation exercise as well as the business process management tool selected to support documentation and communication of technology transfer deliverables. In addition, Chapter 3 summarizes the probability distributions and assumptions used in the discrete event simulation built.

Chapter 4 provides initial findings from the discrete event simulation, including calculation of technology transfer lead times and resource utilization within process development. Chapter 4 also discusses the insights gained from the simulation model, including opportunities for process optimization.

Chapter 5 discusses results from modeling process improvements, and potential efficiencies gained with respect to process lead times and resource utilization. Also presented in Chapter 5 is a case study demonstrating the benefits of discrete event simulation for real-time project tracking and capacity management.

Lastly, **Chapter 6** summarizes the research, including major findings and recommendations for process optimization. Chapter 6 ends with proposals for future work.

1.2 Project Drivers and Motivation

1.2.1 Benefits of Process Optimization in Drug Development

Modern medicine improves the lives of patients worldwide. The influx of new methods of treatment, or treatment modalities, in the last decade gives patients and their families new hopes to treat diseases that were once irrecoverable [1]. The ability for a new therapeutic to reach patients in need is heavily dependent on a successful execution of drug discovery and drug and process development. As the success rate for pipeline molecules to become approved by regulatory agencies and be released commercially is low, the industry must constantly strive to improve both the quality and development time of R&D. Mechanisms for such improvements include capitalizing new discoveries, enhancing business practices and program management, and incorporating new assistive technologies [2].

The development process for therapeutics is no easy feat. The human body is incredibly complex, as are its interactions with external agents. Experts across many disciplines are required for the identification of a molecule that targets specific receptors, characterization of a drug and its pharmacokinetics, and comprehensive testing of a final drug product to ensure safety and efficacy [1]. In addition, the ability to develop a manufacturing process which consistently and reliably produces a molecule and its formulation is critical to enabling commercialization.

Due to the intricacies of therapeutic design considerations, manufacturing sensitivities, and risk to patient safety, regulatory bodies have defined rigorous standards for biopharmaceutical companies to follow when developing new therapeutics. Figure 1-1 outlines the phases of a typical drug development process, starting with basic research and molecule discovery and ending with post-market surveillance after receiving market approval. As depicted in Figure 1-1, the lead time from molecule discovery to market access can take 9.5 to 15 years. During this time, 5,000-10,000 molecules are studied and screened under discovery research, and 600-1100+ patients are tested in clinical trials to measure a product's safety and efficacy [3].

To add to the complexities of biopharmaceutical R&D, the industry is currently facing challenges on the global scale that further impact product development. Although the number of pipeline molecules is increasing, new innovations are offset by low probabilities of obtaining regulatory approval. Furthermore, retiring patents and the influx of biosimilars have shifted product demand from original manufacturers to their cost-effective counterparts. These challenges persist as healthcare costs continue to rise. For these reasons, the biopharmaceutical industry is undergoing increased pressure to further reduce product development and manufacturing costs, resulting in new dependencies that firms place on successful R&D investments and process optimization [4].

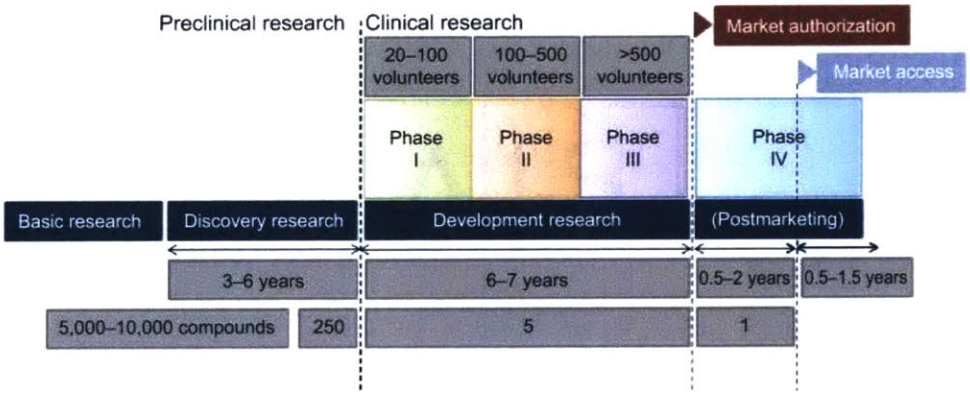

Figure 1-1: *Representation of the Drug Discovery and Development Process [3]*

Figure 1-2 displays the collective probability of receiving Food and Drug Administration (FDA) approval for a new drug after submitting a New Drug Application (NDA) or Biologics License Application (BLA), based on current phase of clinical trials. Although cycles of

technology transfer may occur throughout the drug development cycle, technology transfer to a commercial facility typically begins between late phase 2 and phase 3 of clinical trials where there is an estimated 30%-58% probability of regulatory approval [5]. As such, biopharmaceutical firms operate under a high degree of uncertainty when initiating commercial technology transfer activities, as it is not guaranteed their investment will be returned.

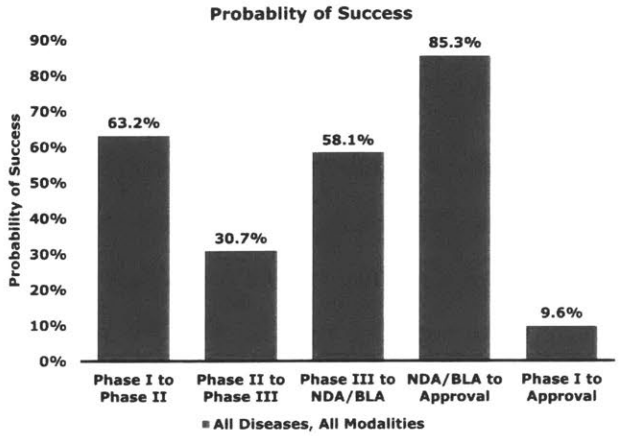

Figure 1-2: *Probability of regulatory approval by clinical trial phase [5]*

Given the attrition rates of molecules in clinical trials and the timelines for commercial technology transfer, it is evident that an efficient tech transfer process reduces the overall financial risk that an organization takes on when initiating transfer activities to a commercial facility. As tech transfer is largely aided by the process development organization, an efficient tech transfer process (assuming no change in resource quantity or capability) is expected to increase the overall capacity of the process development organization. Such capacity increase would result in improved agility and enhance the business's ability to support new molecules entering the pipeline. In addition, an efficient tech transfer process would be more cost effective due to a reduction in time and resources spent on scaling up production. A reduction in lead time further allows an organization to postpone technology transfer until more information is known about the molecule's probability of success, allowing elimination of tech transfer costs for products which fail to advance to licensure.

There exists a secondary and potentially more obvious reason for why firms must strive for an efficient tech transfer process. Drug and process development typically occurs on small-scale production equipment. A drug's critical to quality attributes are sensitive to the manufacturing

environment and are often dependent on process equipment and scale. A case presented by H.J. Federsel highlights the consequence when insights gained from engineering runs at commercial scale required method adjustments during technology transfer [6]. In this case, an alkylation reaction could not be produced in a scaled 4000 l vessel, even though it had successfully completed in laboratory and pilot equipment. It shall be anticipated that similar circumstances may occasionally arise during production scale-up, requiring rapid root cause analysis and process adjustment. An efficient technology transfer process would increase agility of supporting functions, allow the respective teams to effectively respond to process needs while avoiding catastrophic delays to the program. Moreover, it may also provide a means to foresee process risks by allowing parallel development activities to be re-arranged in series.

1.2.2 Business Context: Amgen Background and Enterprise Objectives

Amgen, Inc. is a leading biotechnology companies headquartered in Thousand Oaks, CA. It was incorporated in 1980 as AMGen (Applied Molecular Genetics Inc.). Today, its presence reaches over 100 countries and treats millions of patients globally. Amgen focuses on treatment within the therapeutic categories of cardiovascular disease, oncology, bone health, neuroscience, nephrology, and inflammation. The Process Development organization within Amgen is responsible for the design, qualification, and transfer of production processes and associated engineering and controls throughout the lifecycle of drug production for human use.

Amgen continues to grow the diversity and volume of its commercial product portfolio. To date, Amgen has disclosed 35 molecules across 13 modalities undergoing clinical trials and 8 biosimilars. These products range across 5 therapeutic areas with 50% targeted for hematology/oncology [7]. The Business Monitor International Ltd published the United States Pharmaceuticals and Healthcare Report, citing Amgen's strength of having "one of the most robust drug pipelines within the industry." However, evidence from this report suggests that Amgen is not alone in their quest to maintain a robust product portfolio. Sales of patent drugs are projected to increase by a 5-year compound annual growth rate of 4.1%, highlighting a growing market demand for new therapeutics. [8].

A growing product pipeline can manifest effects across many phases of the drug development lifecycle. As this research is specific to technology transfer, the focus is on the

commercial manufacturing process development. The number of molecules projected to transfer to a manufacturing site increases with respect to a pipeline's size, assuming a constant success rate of products exiting phase 1 and phase 2 clinical trials. Amgen has already observed the effect of a growing pipeline through an increasing trend in number of commercial technology transfers conducted each year. Thus, efforts are being made to optimize business processes and support systems to increase capacity and enhance the efficiency of commercial technology transfer. Such activities are necessary to sustain the rapid growth of products in Amgen's portfolio.

1.3 BACKGROUND

1.3.1 Drug Substance in the Biopharmaceutical Industry

The FDA defines drug substance as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient [14]". A drug substance may be classified as either large or small molecule, which indicates size of the active ingredient as well as its behavior, mode of transportation, and administered form. Small molecules are chemically synthesized organic compounds with well-defined physical properties and molecular weights under 1000 Da. Due to their size, small molecules can often permeate through intestinal epithelial cells, and thus can be administered orally. Conversely, large molecules are biologically produced or engineered with complex physical properties, and have high molecular weights and consequently are usually administered via injection [15].

A biopharmaceutical, also known as a biologic, is a pharmaceutical drug that is produced in or extracted from a biological system. Given the nature of their origin, biopharmaceuticals are distinct from chemically produced small molecules. Most biopharmaceuticals are comprised of large molecule proteins or other biopolymers and are used to prevent, treat, or cure a wide variety of illnesses [9].

The control of biopharmaceutical production is inherently challenging. While small molecules can be manufactured with high consistency using standard chemical processes, the biological systems used to produce large molecules are often highly sensitive to their manufacturing environment. Furthermore, due to the structural complexity of large molecules,

they cannot be characterized using conventional laboratory testing. To ensure consistency in the output of a biopharmaceutical process, a firm must tightly control the biological source, raw materials, and process parameters [10]. The method for producing large molecules is often referred to as biologic manufacturing, or biomanufacturing for short.

1.3.2 Technology Transfer in Biopharmaceutical Industry

The term technology transfer is often used in a variety of contexts. In Intellectual Property (IP) law, technology transfer may be referred to as the transfer of intellectual property from its development location to a secondary location through franchising or licensing. Similarly, technology transfer may refer to the transfer of product knowledge from academic institutions to industry partners for the purpose of commercialization. A review of literature regarding technology transfer in the biopharmaceutical industry yielded a similar breath of definitions and contexts [11]. In this thesis, the focus is on the technology transfer definition specific to manufacturing processes, which occurs between sending and receiving production facilities.

Given technology transfer in the biopharmaceutical industry occurs under a regulated environment, the International Conference on Harmonisation has a specific definition of technology transfer as it pertains to drug manufacturing. This definition as written in ICH Q10 states, "The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement." [12]. Technology transfers may occur across multiple phases for a given drug under development. This study is focused on the final technology transfer to the drug's commercial manufacturing facility in preparation for process validation and manufacturing at-scale.

1.3.3 Technology Transfer for Drug Substance Process Development

Amgen's Drug Substance technology transfer commences upon announcement of the selected commercial manufacturing site for a given program and ends at the start of process performance qualification (PPQ), an essential step of process validation. Although PPQ can only begin after technology transfer is complete, is important to note that technology transfer support may continue through PPQ to ensure successful qualification. Figure 1-3 provides a high-level

depiction of technology transfer scope. Site evaluation is a preceding step involving a full assessment of site capabilities and production capacity across all manufacturing sites. This step must be completed before commercial technology transfer can begin, as initial steps of technology transfer include an in-depth assessment of the chosen commercial (receiving) site against the pilot (sending) site. Technology transfer is considered a success after process performance qualification is completed and the process is proven to consistently and reliably produce product which meets its critical quality attributes (CQAs).

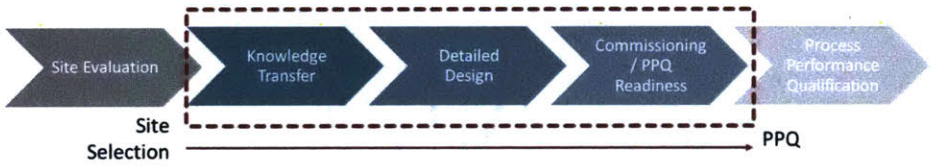

Figure 1-3: *Scope of work as it pertains to commercial Drug Substance technology transfer at Amgen*

Contained within the boundaries of commercial technology transfer are the three essential phases of Knowledge Transfer, Detailed Design, and PPQ Readiness. Knowledge Transfer refers to the translation of information generated from Commercial Process Development (CPD) and Process Characterization (PC) into manufacturing requirements. Often this activity is initiated through a comprehensive gap assessment between small-scale processes and commercial site capabilities. Detailed Design refers to the closure of gaps identified from Knowledge Transfer, which may include additional process characterization studies, bill of material (BOM) revisions, or new equipment installation. Lastly, commissioning / PPQ readiness refers to activities needed to prepare the manufacturing site for process validation. Such steps include equipment commissioning, engineering runs, manufacturing documentation release, and validation master plan approval.

For simplicity, the three technology transfer phases are illustrated in series, as the outputs of the prior phase are used as inputs to the next. Although serial dependencies between the phases certainly exist, in practice activities across multiple phases are often initiated in parallel. For this reason, outputs of a subsequent phase may be created before a prior phase has closed. The dynamic ordering of process steps is discussed in greater detail in Chapter 3 of this thesis. Furthermore, feedback loops exist between knowledge transfer and site-specific process characterization (not

pictured), as well as between process validation and all phases of technology transfer. As this research is focused on technology transfer for Drug Substance Process Development, excluded from the scope of this assessment are technology transfer processes and feedback mechanisms pertaining to product and process testing, such as interactions with attribute sciences.

1.4 Research Methodology and Framework

The study approach is divided into 5 project phases: Map, Simulate, Refine, Analyze, Improve. Given the narrow window of time provided to collect adequate data, the outputs of each phase were developed using an agile process, with continued refinement as additional insights were gained.

1.4.1 Map

The business process of technology transfer was first mapped from site selection (input) to the start of PPQ (output). This phase included value stream mapping of drug substance commercial technology transfer and data collection on required resources and time distributions for process completion. In addition, the information collected was structured and stored in a centralized repository using Promapp software [13], so it could be visualized, reviewed, and modified by the project team to ensure alignment across stakeholders.

1.4.2 Simulate

The business process was modeled in a discrete event simulator using ProModel software [14]. As each technology transfer is unique to the molecule being transferred, the sending and receiving sites, and the personnel responsible for the transfer, a specific program was used as the model archetype. The program was selected for several reasons:

- The transfer was performed recently and thus accurately depicts current state of the process
- The time to complete the technology transfer represented an average completion time based on similar programs running concurrently
- The receiving site is an established facility with prior experience in conducting technology transfers for stainless steel fed-batch processes, recovery, and purification.

1.4.3 Refine

As Amgen is expanding its use of single-use technology in manufacturing, a secondary transfer was analyzed which incorporates single-use technology in its process design. Single-use systems introduce disposable process equipment, offering benefits in manufacturing footprint reduction, production scale flexibility and mobility, and cleaning/changeover costs. This secondary transfer was chosen for comparison against the original architype, which utilized fixed, stainless steel process equipment, to further refine the model for robustness.

1.4.4 Analyze

Lead-time and capacity utilization results from the current state model were analyzed to determine opportunities for workflow optimization. Upon identifying areas for improvement, including current efforts to implement computer-assisted workflows, a future state model was created to calculate impact from proposed process changes.

1.4.5 Improve

The impact of the proposed changes assessed against the overall strain on the enterprise from change management initiatives, including implementation time, capital expenditure, and required full time employee (FTE) hours. A business case was generated to propose improvement measures which improve lead time and resource utilization with considerations to overall effect on the enterprise. In addition, recommendations for future work were provided to realize benefits of methodology on a larger scale.

1.5 Scope of Research

This graduate research project was focused on modeling technology transfer for drug substance process development, from site selection (trigger/input) to process performance qualification (PPQ) initiation (output). As this research project is focused on drug substance, excluded from the scope are technology transfer activities for drug product, final drug product, and attribute sciences. Although not discussed in this report, it is important to note that each of these functional areas undergo technology transfer under their respective processes to support commercialization.

Each business process step was identified and characterized via a review of internal technology transfer records, value stream mapping, and interviews with key stakeholders to identify required resources (people/equipment) and time distributions for activity completion. Once complete, the process was modeled using the discrete event simulation software, ProModel, and results analyzed for continuous improvement opportunities. After consultation with project team members and subject matter experts on feasible optimization techniques, future state models were run to calculate the potential efficiencies gained. The future state model(s) simulate effects of proposed process changes, including those from current initiatives to implement automated workflows and information systems. The efficiencies were evaluated against key performance indicators to ensure successful alignment with overall business objectives.

Chapter 2 Literature Review

2.1 A Brief Overview of Drug Discovery and Development

Drug discovery is the process for which new molecules are identified as potential candidates for therapeutic use. In early-stage drug discovery, a variety of scientific disciplines are required to evaluate molecules for desirable characteristics through laboratory research and benchtop testing. Once candidates are vetted, in vitro experiments are conducted to investigate the safety and efficacy of the molecule in its viable formulations. Information collected during this stage include how the drug is absorbed in the body, the biochemical mechanisms enacted, required dosage, duration of use, pharmacological interactions, and potential side effects [15].

After one or more molecules have been identified, the lead molecule(s) enters pre-clinical studies where it is further evaluated for toxicity. These tests are conducted under controlled environments as mandated by regulatory laws or standards, such as the FDA's Good Laboratory Practices. Once pre-clinical testing is complete, researchers determine whether the molecule is fit to proceed to clinical trials where it will be tested for safety and efficacy in humans [16].

Under United States law governed by the FDA's Code of Federal Regulation Title 21 part 312, clinical investigations are conducted across three sequential studies referred to as Phase 1, Phase 2, and Phase 3. The purpose of Phase 1 is to collect information on the safety and dosage of the drug under evaluation. In this phase, a small patient population of 20-100 healthy individuals receives the drug and is evaluated over several months. Phase 2 studies assess the drug under evaluation for its efficacy and side effects. This phase tests a larger patient population of several hundred individuals who have the targeted disease or condition. Lastly, Phase 3 further evaluates a drug's safety and adverse reactions on a wide patient population. In this phase, several hundred to several thousand patients exhibiting the targeted condition are administered the drug and monitored over the course of one to four years [17]. If the drug has proven safety and efficacy through its pre-clinical and clinical research, it may proceed to filing for regulatory approval. Only if approved may the drug then be marketed for its intended use [18].

2.2 TRENDS IN BIOPHARMACEUTICAL PRODUCT DEVELOPMENT

The biopharmaceutical industry is well known for its extensive product development cycle. The time between drug discovery and product launch can take anywhere from 10 to 15 years [3] and can cost over $1.75 billion [1]. In fact, pharmaceutical companies spend roughly 5 times more on R&D compared to other industries, amounting to 14% to 18% of annual sales [19]. The largest percentage of time and cost spent occurs during clinical trials, which can take 6-7 years for a successful molecule [3].

Despite the resource intensive nature of drug development, only a small number of pipeline molecules reach the commercial market. Fewer than 10% of drugs that enter Phase 1 of clinical trials successfully achieve FDA approval, as illustrated in Figure 1-2. This success rate declines further when accounting for the upstream stage gates in discovery and pre-clinical research. Although the process required to commercially launch a new biopharmaceutical product is certainly demanding on firms, the drug discovery and development process is vital to protecting public health. From early stage discovery to late stage development, each stage has been devised utilizing industry best practices to sift out candidates that could jeopardize the safety of vulnerable patient populations.

With the extensive product development cycle and low probability of approval, one may infer that industry success is restricted in the global marketplace. However, the biopharmaceutical industry has been recognized for its rapid growth in recent years. A study conducted by Allied Market Research cited the 2017 global biopharmaceutical market value at $186,470 million with a compound annual growth rate (CAGR) of 13.8%. This growth is supported by a focus on emerging markets, a rise in monoclonal antibody treatment for chronic diseases, and increasing R&D investments in oncology [20].

2.3 DRUG SUBSTANCE PROCESS DEVELOPMENT

2.3.1 Summary of Drug Substance Manufacturing

In biomanufacturing, the process for producing drug substance is divided into sequential upstream and downstream operations as illustrated in Figure 2-1. Upstream operations include processes related to the growth and expansion of cells used to express the target protein. In a typical fed-batch process, upstream manufacturing begins with a single vial of frozen cells from a

selected cell line which, once thawed, is used to inoculate medium in spinner or shake flasks. Through a controlled series of cell culture and scale-up operations, the cells are grown into larger bioreactors until they reach a terminal reactor where the target protein is expressed. Given the nature of upstream operations, scientists in this field are typically well versed in microbiology, cell culture, and fermenter and bioreactor systems [21].

Downstream operations are focused on the extraction and purification of the harvested drug substance. Although the processes selected for downstream operations may vary depending on the targeted molecule, required steps generally include filtration and column chromatography. The diagram shown in Figure 2-1 also includes a refolding operation, which is not typical in monoclonal antibody production. Downstream scientists are typically well versed in chemistry, chromatography, tangential flow filtration (TFF), and other filtration systems [21].

Throughout upstream and downstream manufacturing are various mechanisms for quality control and process monitoring. To ensure consistent product integrity, material samples are extracted at designated points within the manufacturing process for analytical testing. Assays are often used in combination with validated test methods to analyze samples for specific quality attributes. In addition to product testing, the manufacturing process is continuously monitored to ensure adherence to specified control limits. Parameters measured include, but are not limited to, pH, temperature, pressure, flow rates, pO_2, and pCO_2 [22].

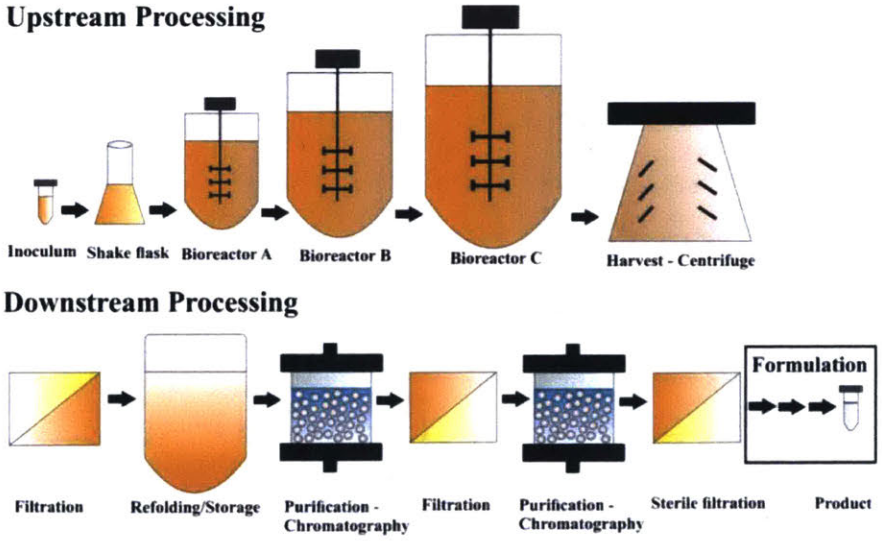

Figure 2-1: *Simplified workflow for a biomanufacturing process [23]*

2.3.2 Drug Substance Process Development

In Biotechnology, Drug Substance Process Development is the discipline of developing the upstream and downstream manufacturing processes for a given biologic. It includes the identification of process steps and their corresponding parameters needed to produce a specified molecule at a target yield. Process Development organizations are often engaged early in drug development to design and scale a manufacturing process suitable to support clinical trials and subsequent commercial supply. Once the commercial manufacturing process has been transferred and validated, modifications must undergo thorough assessments, and often regulatory reviews, to ensure changes do not impact product integrity. For this reason, the output of process development is crucial to preparing a program for both initial and long-term success.

The Process Development organization for Drug Substance within Amgen is divided into Pre-Pivotal Process Development, Pivotal Process Development, and Drug Substance Technologies & Engineering. The Pre-pivotal Drug Substance Technologies group supports clinical drug substance manufacturing for early stage programs within Amgen's pipeline. Likewise, the Pivotal Drug Substance Technologies group supports the development and characterization of manufacturing processes for late stage programs. Lastly, process engineering and commercial technology transfer are driven by the Drug Substance Technologies and Engineering group in support of product commercialization.

2.3.3 Considerations for Commercial Scale-Up

Technology transfer is a critical component of product commercialization. It is not only a transfer of manufacturing procedures, but it is a sharing of process knowledge required to manufacture product that meets quality, reliability, and repeatability standards. A successful technology transfer requires coordination between development and manufacturing and across sending and receiving sites. Resources regularly involved in technology transfer may include personnel from Process Development, Manufacturing, Facilities and Equipment, Attribute Sciences, Quality and Regulatory, Validation Engineering, and more. As technology transfer involves a variety of disciplines, both technical and management expertise are required to successfully compile and disseminate information across participating functions.

2.4 Factors Influencing Process Development Productivity

2.4.1 Key Drivers for a Successful Technology Transfer

The BioPhorum Operations Group (BPOG) is a cross-industry collaboration focused on advancing biopharma operations. Currently there are over 60 member companies of BPOG representing Biopharmaceutical Developers, Manufacturers & Suppliers, including Amgen, Roche, GE Healthcare, and Pall Life Sciences [24]. In 2015, the member companies of the BioPhorum Operations Group identified a need to benchmark best practices for technology transfers. They observed misalignments in terminology, milestones, and metrics across the biopharmaceutical industry and sought to define a set of standard language and tools which could be used to collectively improve the technology transfer process. Their assessment concluded three categories of drivers for successful technology transfers, shown in Figure 2-2 [25].

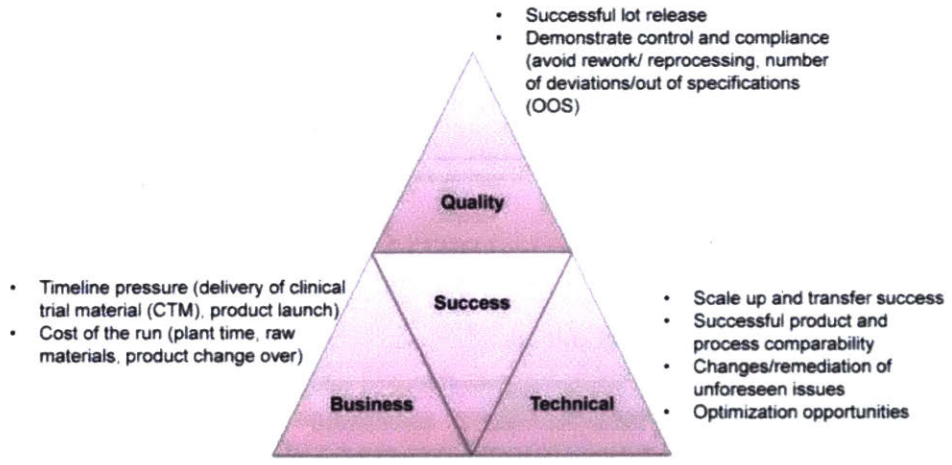

Figure 2-2: *Key drivers for successful technology transfers in biopharmaceuticals [25]*

The member companies of BPOG compiled a list of stages and milestones required for a successful technology transfer. Per their assessment, technology transfer commences upon identification of the receiving site and finishes after a successful pre-approval inspection and subsequent licensure approval. Between the starting and ending gates, BPOG found that successful technology transfers include a process transfer initiation phase where gap assessments are conducted and information exchange begins. This phase is followed by process transfer execution, where manufacturing dry runs are conducted and the process performance qualification (PPQ) preparation work is performed. Lastly, a successful PPQ campaign must follow process

transfer to signal process transfer completion. Only after a successful PPQ campaign is completed may submission and licensure commence [25].

Figure 2-3 shows the extracted highlights of their assessment. Listed under each stage are critical milestones supporting stage completion. It is important to note that this assessment defines technology transfer as extending beyond the boundaries of our study. For the purposes of our evaluation, we assessed technology transfer activities through the start of Process Performance Qualification (PPQ), as activities conducted prior to PPQ are led by Process Development and supported by other functions as needed. In addition, we did not include analytical transfer activities as part of our evaluation.

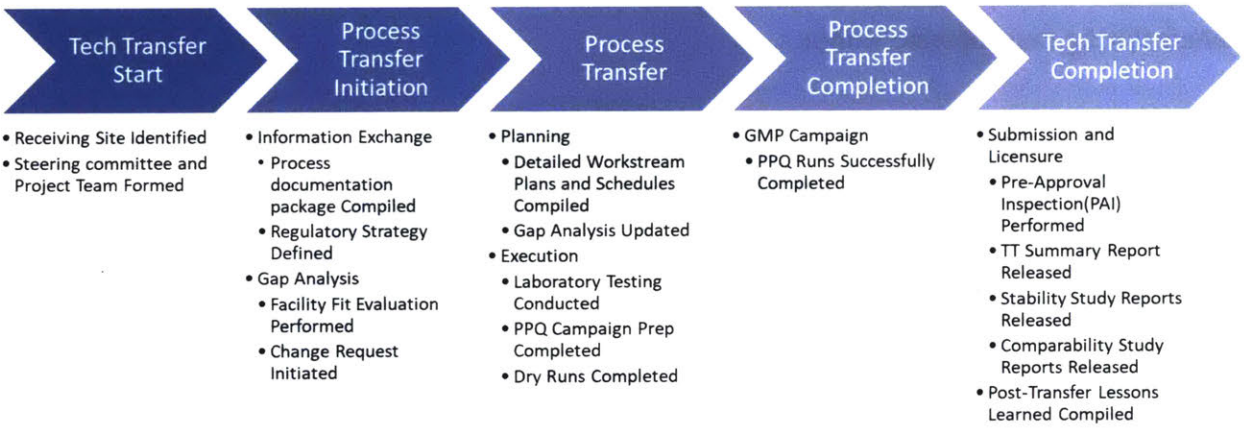

Figure 2-3: *Identified Stages and Milestones for Biopharmaceutical Technology Transfers [25]*

2.4.2 Quality by Design

Quality by Design is a notion first coined by the quality professional, Joseph Juran, in his book, *Juran on Quality by Design*. Juran believed that product quality could be ensured through proper planning, control, and improvement throughout a product's lifecycle. The foundation of his principles support applications in industrial engineering and have integrated broadly into Lean Manufacturing and Six Sigma curricula [26]. In 2004, the FDA released a guidance document titled, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance", intended to promote Quality by Design principles to assure the safety and effectiveness of pharmaceutical products for their intended use. On November 10, 2005, the International Council for Harmonisation, an organization comprised of regulatory and industry experts focused on developing guidelines to harmonize global pharmaceutical requirements,

followed the FDA's adoption by releasing annex ICH Q8(R2), a guidance document supporting pharmaceutical discovery, development, and manufacturing [27].

Quality by Design (QbD) for the pharmaceutical industry is a systematic approach to assuring quality through drug development and manufacturing. It begins with the identification of the Target Quality Product Profile, or TQPP, which is used as a basis for the product development strategy. The TQPP outlines the performance-based attributes that a product must exhibit in order to meet its clinical objectives. The criteria outlined in the TQPP serve as the foundation for critical to quality attributes (CQA), Critical Process Parameters (CPP), and the product's control strategy [28]. These parameters define the design space to which drug discovery, development, and manufacturing must operate within.

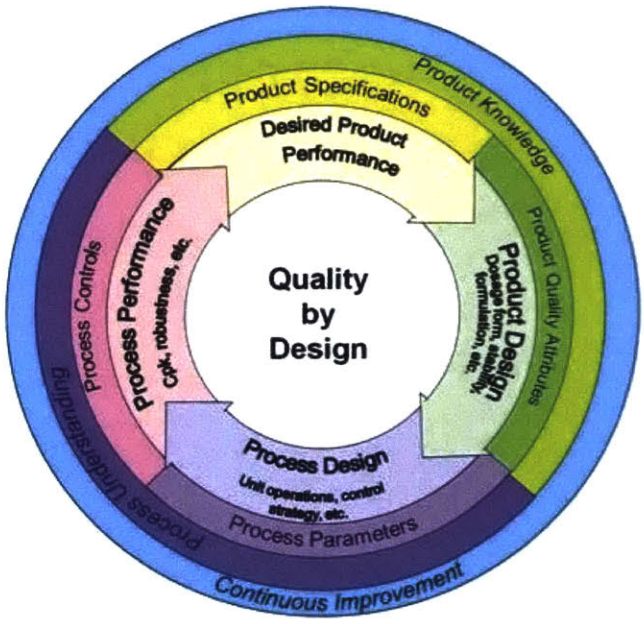

Figure 2-4: *Quality by Design principles outlined by the Food and Drug Administration*

Applications of Quality-by-Design principles can support commercial technology transfer through multiple angles. A critical step in the technology transfer process is the identification of process and equipment gaps between the sending and receiving sites. The gaps identified may be due to misalignments in available equipment, scale, or operating parameters. The risk assessments developed within the Quality-by-Design framework inform mitigation strategies for identified gaps and allow for a risk-based approach to be used. This results in an increase in process efficiency as well as a heightened focus on areas critical to maintaining product quality.

In addition to promoting a risk-based approach to gap mitigations, quality-by-design principles support strategies for process characterization and validation. With the knowledge gained from the use of Quality by Design, firms can better predict the impact of process changes with fewer studies conducted at commercial scale. This shift in focus allows firms to save a considerable amount of time, raw materials, and resources. Lastly, through the systematic assessment, documentation, and review of product attributes and process parameters, Quality by Design promotes heightened communication and knowledge sharing across functions [29].

2.4.3 Lean Applications

Lean Manufacturing is a systematic method for identifying and eliminating waste within an operations system. It was most notably adopted by the Japanese manufacturing industry with the advent of the Toyota Production System, and later popularized in the early 1990s after the publishing of *The Machine That Changed the World.* The purpose of Lean is to eliminate categories of waste through enhancing visibility, thereby improving product quality, productivity, cost, and customer satisfaction. Since its conception, Lean principles have been adapted to continuously improve systems across enterprises through a "Lean Thinking" approach. In this thesis, the focus is on lean principles as they relate to biopharmaceutical development and manufacturing.

Lean is focused on designing customer-centric operations. A lean system delivers only what is needed by the customer, when it is needed, utilizing efficient production processes. This is performed through the elimination of eight types of wastes, or "muda", as shown in Figure 2-5.

Jugulum and Samuel related each category of waste to business process contexts supporting product design (ee Table 2-1 for a summary of applicable examples to the technology transfer business process, which will be analyzed further in Chapter 5). Techniques used to identify and eliminate these areas of waste include mistake-proofing, visual management, implementing standardized work, value stream mapping, and Kaizen (otherwise known as continuous improvement) [30].

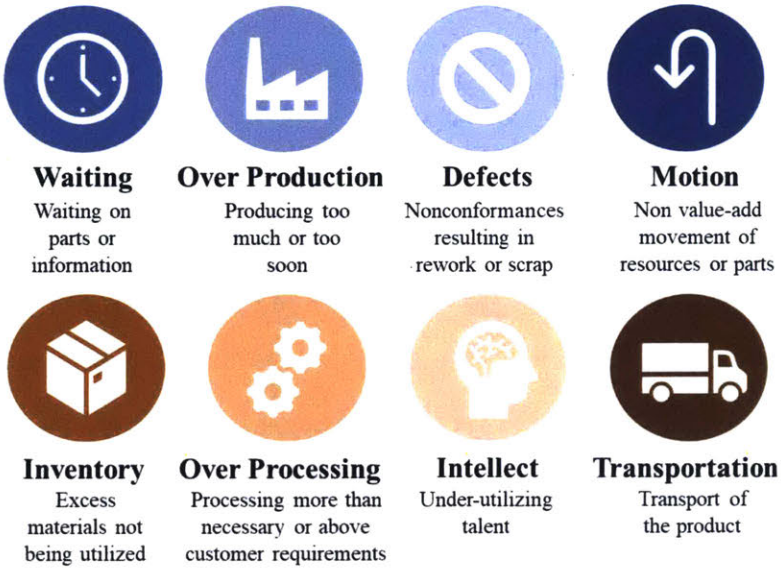

Figure 2-5: *Illustration of eight wastes adapted from John Wiley & Sons, Inc: Design for Lean Six Sigma [30]*

Waste	**Business Process Context**
Waiting	Documents waiting for review, approval, or processing
Over Production	Providing too much information in a report or deliverable
Defects	Revising documents or other program deliverables
Motion	Placement of information in inconvenient locations for users
Over Processing	Performing steps or analysis that are not required by customer, such as non-value add steps in an engineering change order
Inventory	Physical storage of raw materials, WIP, and finished goods
Intellect	Poor communication and failure to engage employees in ideation and continuous improvement
Transportation	Unnecessary movement of inventory between process steps

Table 2-1: *Examples of waste within business processes*

An article published in Contract Pharma by Snee et al. [31] explored applications of Quality by Design and Lean Six Sigma for biopharmaceutical technology transfer. the article cited an example of technology transfer within a major pharmaceutical company to highlight challenges companies faced when conducting technology transfer. In the case study presented, the company announced a decision to close five manufacturing plants and transfer existing products to global facilities and contract manufacturers. However, six months into the project, progress was minimal. No products had been transferred, one of the five plant managers left, contract manufacturing agreements had not yet been signed, and there was a lack of clear understanding of impending transfers and responsibilities of supporting teams [31].

In a similar fashion to Quality by Design, Snee et al. explored a "transfer space", defining the critical attributes of a project which drives its success. The transfer space includes a framework of technology transfer requirements, activities, and decision points to systematically manage technology transfer products and drive success. Critical success factors included active senior management leadership, clear definition of success, creation and use of process understanding, use of statistical modeling, supporting infrastructure with defined responsibilities and adequate staffing, and a clear financial focus. Furthermore, 10 process steps were provided to guide transfer teams in defining technology transfer processes and investigating issues as they arise. These 10 steps included [31]:

1.) Determine scope, strategy and risk

2.) Identify gaps between project management capabilities and requirements

3.) Develop a body of governance, champion and mentors

4.) Define communication and reporting channels

5.) Define performance metrics

6.) Develop and train transfer teams

7.) Conduct gap analysis for each product between sending and receiving sites

8.) Define responsibilities for supporting groups and individual roles

9.) Determine a transfer strategy for each product based on gap analyses

10.) Actively manage activities via individual and program management reviews

Another article published in 2009 explored applications of Lean within the biopharmaceutical industry. Stoll et al. [20] presented three cases of Lean implementation within a major biopharmaceutical company, Novartis, to improve throughput rate, cycle time, failure rate, and capacity utilization. In one of the three case studies presented, Lean principles were applied to accelerate the generation of batch record templates for a large-scale cell culture suite in support of technology transfer activities. Through the use of generic templates, elimination of redundant information and intermediate protocols, instilling regular check-ins, and ensuring a strict monitoring of timelines, batch record generation was reduced from fourteen days to seven days using the same manpower. In addition, document size reduced by 25% and the organization observed an enhanced understanding of transfer requirements and responsibilities, resulting in faster response-rates to critical issues and an improved adherence to project schedules [32].

2.5 Process Modeling and Simulation in Industry

Processes often involve the transport of entities (materials or goods) through sequential operations, where each entity is processed or assembled into a new state. The flow of entities can be characterized by the cycle times of the individual operations, the arrival time of entities into the process, and the number of work in process entities within the system. If the number of work-in-process entities exceeds a system's processing capacity, then queuing will begin and lead times will extend. Such process phenomenon can also occur for intangible entities, such as data or information, if the resources needed to process them are limited. Sections 2.5.1-2.5.2 describe relevant methods for modeling process behavior. Furthermore, these sections discuss how the modeling techniques can be used to characterize the flow of intangible entities within the commercial technology transfer business process.

2.5.1 Productivity Modeling

Little's law is widely used in queuing theory to relate wait time, arrival rates, and queue size within a system. Little's Law states that any steady state process must satisfy

$$L = \lambda W$$

***Equation 2-1**: Little's law, where L = number of units in system, W = time spent by a unit in the system, and $1/\lambda$ = time between two consecutive arrivals* [33].

A variation of Little's law was adapted by Hopp and Spearman to model inventory flow in a production system [34]. This variation relates Work in Process (WIP), Throughput (λ), and Cycle Time (CT), by

$$\lambda = \frac{WIP}{CT}$$

***Equation 2-2**: Little's law adapted for Operations Management, where WIP = inventory being processed, λ = average output of process per a unit of time, and CT = time a part spends as WIP within the system.*

The main difference between Little's law and Hopp and Spearman's adaptation is the representation of the rate λ. In the context of queuing, λ represents arrival rates, while in operations modeling, λ represents output rate. Equation 2-2 demonstrates that a system's throughput can be managed through the control of *WIP* and cycle time. Thus, throughput can be enhanced by optimizing *WIP* counts and *CT* using process design and capacity management techniques.

In the context of technology transfer, tasks often wait for a free resource to be acted upon. Thus, tasks arriving to a resource for processing can be modeled with queuing theory. Using this approach, the resource acts as the server, and awaiting tasks as the customer. Equating the variables in Little's law, L = total number of tasks waiting to be processed by the server, W = time the task spent in the system, and λ = arrival rate of tasks into the server's queue. Assuming both a general arrival rate and a general service rate, the mean waiting time can be approximated using Kingman's formula [35]

$$E[W_q] \approx \frac{C_A^2 + C_S^2}{2} \frac{\rho}{1-\rho} E[S]$$

***Equation 2-3:** general server (G/G/1) model to calculate wait time for item in queue, where $E[W_q]$ = mean wait time in queue, C_A = coefficient of variation for arrivals, C_S = coefficient of variation for service time, ρ = utilization of server, and E[S] = mean service time.*

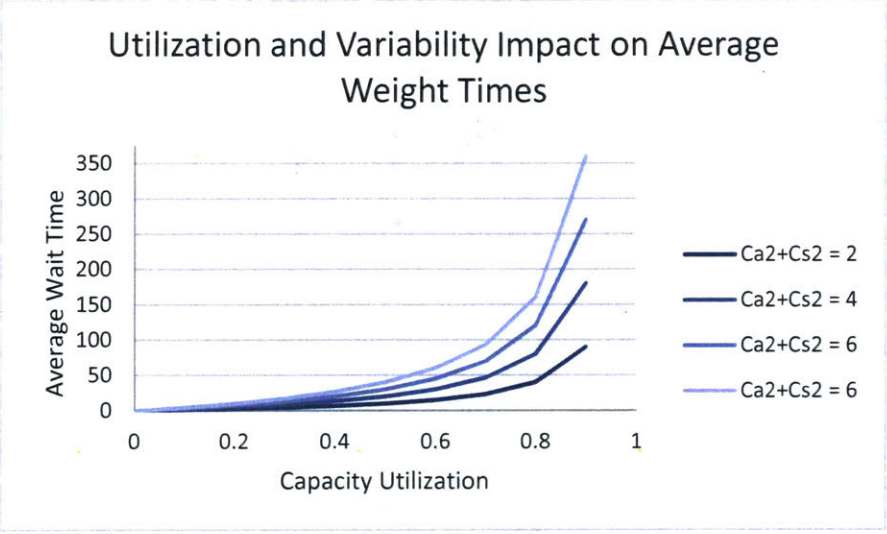

Figure 2-6: *Graph of average wait times with respect to coefficients of variation and capacity utilization*

As depicted in Figure 2-6, the average weight time increases exponentially with capacity utilization and linearly with the sum of the squares of coefficients of variation.

A main key performance indicator (KPI) in the technology transfer process is the end-to-end cycle time for conducting a technology transfer, that is, the cumulative time between initiating a technology transfer and completing a technology transfer for a given program. In a scenario where unlimited resources exist to carry out tasks, the cycle times for a population of technology transfer programs may be assumed to be independent and identically distributed. Under this assumption, any two programs within the set must satisfy

$$P(x_1) \text{ and } P(x_2) = P(x_1)\,P(x_2)$$

Equation 2-4: *Probability equation for independent events* [36]

$$P(x_2|x_1) = P(x_2)$$

Equation 2-5: *Probability equation for conditional independence* [36]

Under the central limit theorem, with a large enough population of technology transfer programs ($k \to \infty$), the probability distribution of average lead times within a given set of size n converges to a normal distribution, centered at the mean of the total population[37].

In practice, technology transfers are not completely independent of each other. Due to constraints in both equipment and personnel supporting transfer activities, programs running concurrently compete for the same resources. Thus, challenges or delays in one program have the potential to impact lead times of another due to the consumption of available resources and subsequent queuing of tasks. This effect is amplified when resource utilization and/or variability in task arrival increases. Therefore, we turn to discrete event simulation to characterize the dynamics of the process workflow.

2.5.2 Discrete Event Simulation Applications in Industry

For complex systems, sophisticated tools are often called upon to aid in process design, analysis, and improvement. In particular, Discrete Event Simulation is a widely used tool to analyze phenomena such as queuing, resource utilization, and throughput to plan or improve an operations system. Discrete Event Simulation models the state change of a system within a discrete point in time as it moves through a systematic sequence of process events. Stochasticity can be injected into discrete event simulations through assignment of probability distributions, thus allowing detailed analysis of process variation. In industry, discrete event simulation is used to model schemes such as manufacturing workflow, inventory and distribution systems, transportation networks, and healthcare delivery systems [38].

As our work applies discrete event simulation to information flow, we reviewed industry applications of discrete event simulation for decision support and business process management. A study conducted at Cranfield University reviewed applications of discrete event simulation for dynamic decision making in biopharmaceutical process development. Specifically, the model was built to simulate various scenarios of media prep for cell culture of a gene therapy product. The objective of the study was to model both current state of the manufacturing process to measure cycle times, capacity utilization, and cost, and compare KPIs against proposed future state models. Through discrete event simulation, the authors identified a potential 50% reduction in end to end cycle time, 33% reduction in resources required, and a 25% increase in operator utilization. The study demonstrated the value of applying models and computer-aided tools for decision support systems in the biopharmaceutical industry [39].

An article published in the Journal of Simulation summarized an analysis performed on the benefits and obstacles for using discrete event simulation to aid in business process management [24]. The article reports that discrete event simulation can provide insights into variability and resource utilization for newly designed processes which are not yet fully understood. In addition, discrete event simulation can capture the stochasticity of business processes and resource behavior that cannot be represented in static flowcharting tools. However, Hlupic noted that simulation is not widely used for business process modeling, possibly due to the lack of simulation tools available, or more importantly, the lack of awareness of simulation within the business community [40].

Chapter 3 Research Methodology

3.1 Characterization of Technology Transfer

Technology transfer is intrinsically complex. A successful technology transfer requires clear objectives, knowledge sharing across functions and sites, and organizational agility to address transfer needs as they arise. Early stage technology transfer activities initiate a multitude of processes, often run in parallel, that are managed by the transfer team. As discrete event simulation requires a technical understanding of the activities involved, the characterization of process steps and dependencies is essential to ensuring an accurate and complete model design.

To define the technology transfer process for Drug Substance Process Development at Amgen, we first aligned ourselves to Amgen's requirements and standards. This alignment was performed through a thorough assessment of quality documentation, including standard operating procedures (SOPs) and program records, as well as process maps and organizational RACI charts used within Drug Substance Technologies and Engineering. The results of this review were augmented through personnel interviews with subject matter experts who have been involved in recent technology transfers at Amgen.

Through this assessment, it was identified that technology transfer deliverables vary greatly depending on the program being transferred. Considerations impacting the technology transfer workflow included the sending and receiving sites involved, manufacturing environments, modality of molecules, and maturity of the technology transfer teams. Thus, we determined that the best approach for modeling the process was to use a recently completed transfer as an "architype" to base our initial model from. After collecting data on the base-case transfer, a secondary transfer would then be used as a comparison measure to further refine the model for robustness.

The architype selected was a domestic technology transfer for a monoclonal antibody produced using traditional fed-batch operations. We chose the architype based on three criteria:

1.) The transfer was performed recently and thus accurately depicts the current state of the process.

2.) The time to complete the technology transfer represented an average completion time based on similar programs running concurrently.

3.) The receiving site is an established facility with prior experience in conducting similar technology transfers.

The secondary transfer selected involved an international receiving site with single use technology manufacturing. This secondary architype was chosen as it reflected a transfer with additional complexities and thus would shed new insights on process requirements.

3.2 Methods of Data Collection And Storage

An abundance of information is required to build an accurate model of the commercial technology transfer process. Before acquiring this information, we had to identify the scope and depth of our data collection. This was performed through the mapping and analysis of technology transfer workflows with respect to process activities, required deliverables, and sequence of events.

Our first step in data collection was to conduct a value stream mapping session of the technology transfer process with a cross functional team. Included in this workshop were members from Drug Substance Technologies and Engineering, Pivotal Drug Substance, Facilities and Equipment Project Management, Manufacturing Engineering, and Validation. The team was divided into three groups assigned to a specific technology transfer phase. We instructed teams to build value stream maps utilizing rudimentary tools such as white boards and post-it notes to promote collaboration and engagement. At the end of the session, an integrated set of process maps was completed and agreed upon by the cross-functional team. Each map outlined the sequence of required activities within a given phase and responsible parties involved.

The compiled process workflows were transferred to the business process management software, Promapp, for additional refinement. Simultaneously, additional data were collected to support the characterization of each process step for the discrete event simulation. Information collected included:

1.) Technology Transfer demands and forecasts

2.) FTE's, holidays, and shifts

3.) Resources (people/equipment) utilized within each process step

4.) Activity times for step completion and their distributions

5.) Average review and approval times for document deliverables

6.) Counts of individual deliverables generated, such as process characterization runs, gaps identified, or protocols released

7.) Percentage of deliverables reworked and common rework pathways

8.) Process dependencies not readily obvious from established workflows

Data collection was conducted over a period of several months. We acquired touch times for 100+ technology transfer deliverables through a review of timestamps in Amgen's document control system for quality records. In addition, we reviewed nearly 2,800 Microsoft project tasks and forecasts to understand both projected and measured activity times. Lastly, over 20 technology transfer subject matter experts were consulted to verify information gathered and further quantify resource involvement.

A Microsoft Access database was created to record and organize our data. The database was comprised of four main tables which stored information collected through project schedules, deliverable reviews and personnel interviews. Figure 3-1 shows the relation of three tables in a simple query, designed to report average deliverable counts and cycle times linked to attributes in the model input. The fourth table was used in conjunction with the process model software, StatFit [41], to identify distributions around cycle times.

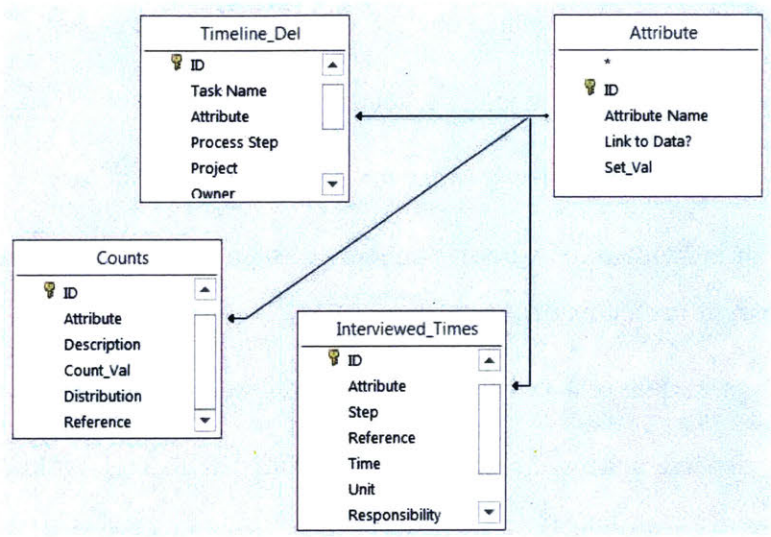

***Figure 3-1**: A simple relationship map between Access Tables to query data for input to the discrete event simulation*

3.3 Business Process Management Tools for Information Storage, Sharing, and Retrieval

To effectively model the Technology Transfer business process and obtain agreement on improvement initiatives, a current state workflow must be established and modified collaboratively with a project team. In our early stages of data collection, we identified the need for a sophisticated business process management tool to aid in this effort. Requirements for this tool included intuitive visualization of hierarchical workflows, links to databases and/or document files, and a collaborative cloud-based interface for teams to store and share information.

Through our evaluation, we identified the business process management software, Promapp, as suitable for our needs. Benefits of Promapp's software included:

1.) Intuitive process mapping and visualization that can be shared across an enterprise

2.) Capabilities to link business process elements to process data, such as resources utilized and time study information.

3.) Collaborative interface for cross functional teams to review, edit, and approve workflow streams from a centralized repository.

Figure 3-2 demonstrates the user interface for a given process within Promapp. Documented within each activity are process steps detailing how the work is completed. In addition, relevant links to supplementary information, quality procedures, or standard templates are provided. For confidentiality, information pertaining to cycle times and proprietary systems are redacted from the screenshot.

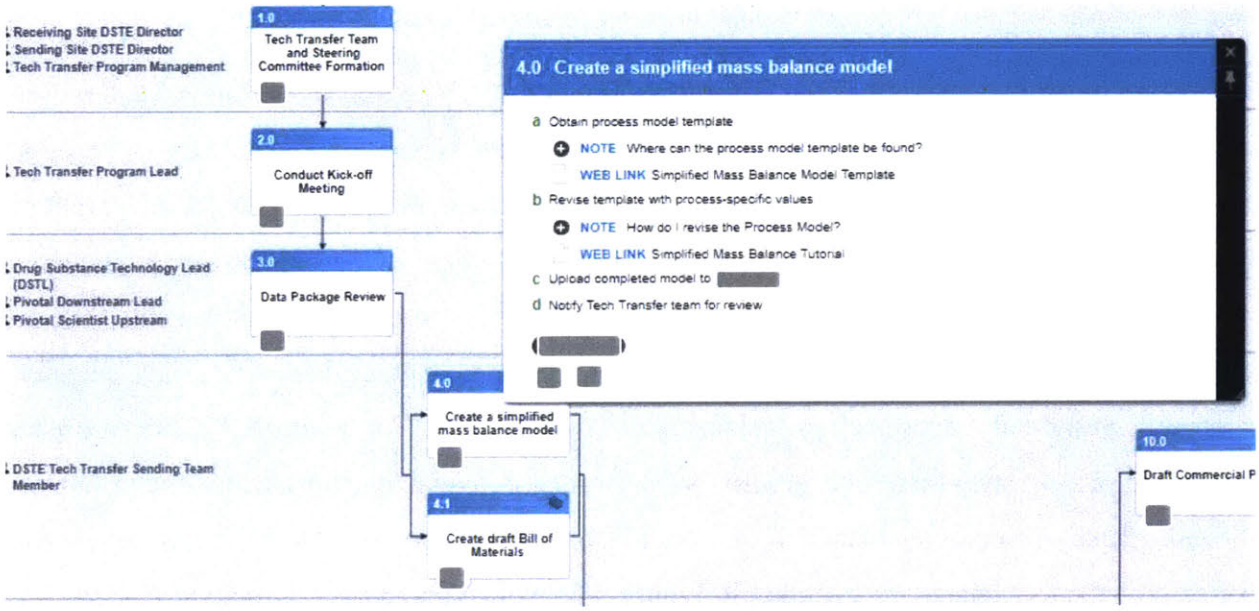

Figure 3-2: *Screenshot of Promapp software used to support knowledge sharing of technology transfer workflows*

3.4 SIMULATION DESIGN AND ARCHITECTURE

The discrete event simulation software, ProModel, was used to model the technology transfer process for drug substance process development. ProModel provides an interface to visualize workstreams and perform scenario analysis to evaluate process impact on identified KPIs. Typically, ProModel is used to plan, design, or improve an operations or logistics system. However, we catered the functionality of the software to support business process modeling.

ProModel's discrete event simulation uses entities, locations, resources, and process routes to characterize operations. Entities are items which are processed within the system. In a manufacturing environment, an entity may be a raw material or assembly which is manipulated,

batched, or transformed at specific stages within the process. Entities are often assigned attributes which contain numerical information regarding that entity. Attributes specify characteristics of an entity and may be acted upon in process logic.

Locations are defined as the places, whether physical or virtual, in which entities are handled. Locations often contain designated resources in the form of people or equipment used to process entities. Shift assignments may be provided to control a resource's operating window. Process logic defines the sequence of locations that an entity travels as it moves through the system.

The simulation was designed to model the flow of technology transfer information through a series of business process events. Thus, entities reflected the generation and delivery of process information (raw materials) that could be combined to produce technology transfer deliverables (assemblies). Examples of entities flowing through the model include process requirements, receiving site capabilities, identified gaps from knowledge transfer, risk assessments, and a program's control strategy. Entities are assigned attributes that define technology transfer parameters, randomly chosen from a specified distribution. These attributes are used to characterize a program with respect to activity cycle times, deliverable requirements, and resources utilized. These attributes are specified in a csv file which is called upon model initialization. An example of the csv inputs are included in Figure 3-3, with proprietary information masked for confidentiality.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Entity	Location	Qty	Time	Number	Freq	ASTL	C_Comissioning_F	C_MaB_Gaps_Ir	C_MaB_Gaps_In	C_MaB_Gaps_New	C_MaB_Gaps_	C_MBR_
2	Site_Selection_Memo	Team_Form_and_Data_Review	1	0	X	N(a,b) wk	0	U(a,b)	U(a,b)	U(a,b)	X	X	U(a,b)
3													
4													
5													
6													

Figure 3-3: *Example format of initialization file, with arrival entity and associated attributes*

The locations are defined as virtual process activity steps where entities (information and deliverables) are processed. Locations utilize personnel within the defined technology transfer team and supporting functions. In a small number of steps, locations also utilize capital equipment for the processing and testing of physical material to aid information generation. For consistency, we designed locations to closely align to activity steps documented in our technology transfer workflows in Promapp.

Resources were selected to reflect technology transfer teams and support functions across sending and receiving sites within drug substance process development. The model assumes that Drug Substance Technology and Engineering have a finite capacity of [X] teams to which can be assigned technology transfer programs on a rolling basis. Resources are assigned shifts to reflect an eight hour workday five days a week, with Amgen holidays and shutdown periods accounted for. The shifts are also adjusted to reflect a resource's geographic location and operating time zone. These adjustments were made in reference to Eastern Standard Time.

Entities flow through locations per a specified routing sequence. As entities reflect information or deliverables generated throughout the technology transfer process, most entities arrive only after the completion of a process step. When an activity produces new information required for downstream processing, its location will order the respective entity to enter the model. Furthermore, when one or more categories of information is utilized in the generation of a deliverable, the model simulates the assembly of information and proceeds with the transformed output.

The simulation model is comprised of 51 entities with 26 attributes, 99 locations, and 42 resources. A screenshot of the model interface and sample processing code are provided in Figures 3-4 and 3-5. Unlike most manufacturing processes or distribution systems, information may feed multiple parallel pathways, and thus cannot be depicted using a single workflow stream. For that reason, connections between process steps are not always visible via routing arrows. These connections certainly exist, however, and can be traced in the processing code.

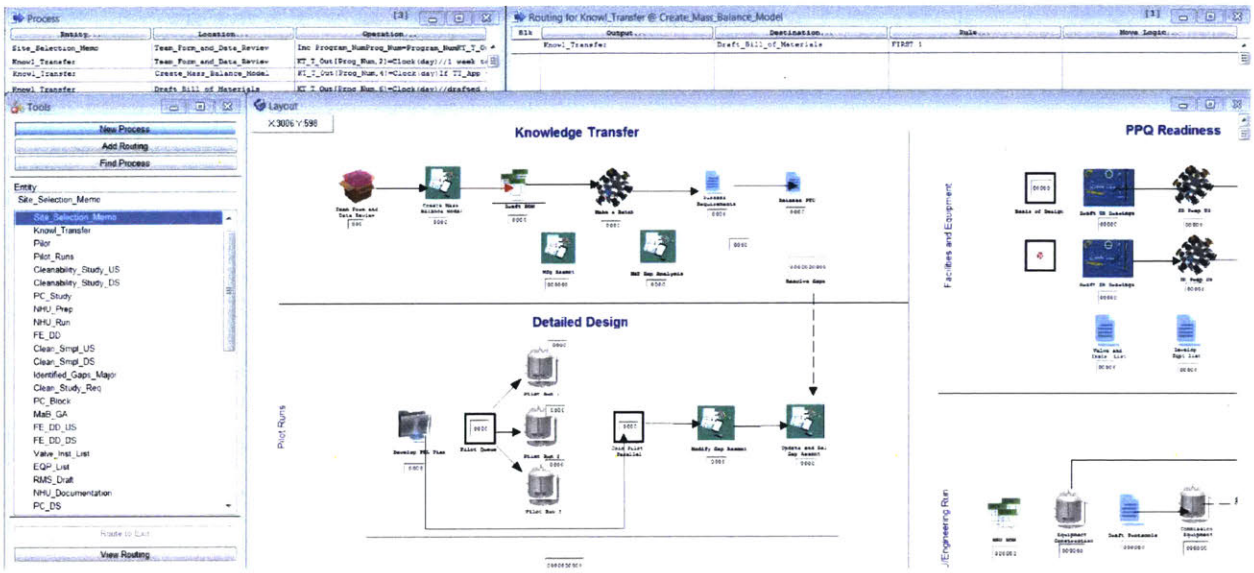

Figure 3-4: *Screenshot of Technology Transfer simulation in Promodel*

```
PC_Out[Prog_Num,11]=Clock(day)

//ENTER RESULTS
Int y = 0
While y < T_ELN_Entry Do
{
    Use 1 res(PD_DST_Scientist) For N(1,1) hr
    Inc y
}


PC_Out[Prog_Num,12]=Clock(day)

Int num=PC_Out[Prog_Num,13]
Inc num
PC_Out[Prog_Num,13]=num

//IF ALL ENTRIES ARE COMPLETE, ORDER SUMMARY REPORTS

If PC_Out[Prog_Num,32]=1 And PC_Out[Prog_Num,33]=0 Then
{
    Order US_PC_Sum_RPT PC_Sum_Rpt_US To PC_Summary_Report
    PC_Out[Prog_Num,33]=1
}

If PC_Out[Prog_Num,17]>0 and  PC_Out[Prog_Num,34]=0 Then
{
    Order DS_PC_Sum_RPT PC_Sum_Rpt_DS To PC_Summary_Report
     PC_Out[Prog_Num,34]=1
}
```

Figure 3-5: *Sample processing code*

3.5 DISTRIBUTIONS AND MODEL ASSUMPTIONS

Distributions were used to characterize variability within the technology transfer process. Typically, cycle times for process steps were assigned a distribution based on data collected. The data fitting program, StatFit, was used to select the optimal distribution for a given dataset. Beta distributions were often chosen from StatFit to characterize the time needed to review a

deliverable, as this distribution accounted for a zero probability that a review period is measured in <0 days, while allowing occasional outliers of reviews to exceeding 2x-3x of the standard deviation. The resulting right skewed distribution of review is seen in practice due to external pressure on resources or a decline in priory.

In certain situations, entity counts were also characterized via a distribution to introduce stochasticity into the model behavior. For example, the number of gaps identified during the site capabilities gap assessment is expected to differ by program. To simulate this variability, the number of simulated gaps were chosen from a uniform distribution, which was specified based on the information we gathered from the two architype programs studied. Where a large enough dataset was not readily available to fit a distribution around cycle times, we assumed that the data followed a normal distribution with variance equal to the square root of its mean. Through the random selection of process parameters within a specified distribution, the model can serve as a Monte Carlo assessment of technology transfer KPIs.

Business processes differ from operations or logistics systems in that resources are not dedicated to a single task for the entire duration of that task. For example, resources in a business process may have multiple tasks to complete at the same time, resulting in the need to prioritize which to perform first based on business need, or in some cases, personal preference. In addition, tasks assigned to a resource may take hours, days, or weeks to complete, rather than orders of seconds or minutes which are typically observed in manufacturing operations. For this reason, we needed to design our simulation to model human behavior for task prioritization and completion.

To simplify our model, we assumed that resources followed a first in first out order of activity completion, based on the time at which tasks arrived in their queue. In addition, we assumed that any task requiring more than two hours of a resource's time would be completed in one hour intervals. That is, a resource would be fully dedicated to a given task for one hour, at which point the resource would decide to continue working on the task or switch to another task in its queue. This structure had two major benefits with respect to the simulation accuracy. First, through this design the simulation introduced a controlled level of randomness to how resources complete their work, representing true behavior of employees prioritizing work within a business process. Second, this design allowed for resources to be momentarily freed from their work at most every two hours, allowing for them to pause for designated downtimes or end their shift.

3.6 SENSITIVITY ANALYSIS

To support model validation, a sensitivity analysis was performed on all parameters which meet select inclusion criteria on our baseline model (without process improvement adjustments). The sensitivity analysis demonstrates the uncertainty of the discrete event simulation model based on the uncertainty of its inputs. Inclusion criteria for the sensitivity analysis included:

1.) Parameter must represent a cycle time for activity completion, including:

   a. Time resource is utilized to perform a step

   b. Average time an entity waits on an external force (such as a resource endorsement or process step outside scope of model)

   c. Time needed to review/approve key deliverables

2.) Parameter must represent a time period $\geq$ 4 hours

The sensitivity analysis assessed the impact on the overall end-to-end technology transfer lead time from the individual adjustment of each parameter by +40 hours, or 1 business week. This time was chosen to amplify effects of each adjusted parameter, as an adjustment <40 hours may not show any noticeable effect on the model results, given the measured endpoint. In addition, a 40-hour window of uncertainty follows a logical explanation of variability, accounting for possible resource sick time, vacations, and/or priority shifts.

Table 3-1 lists the result of the sensitivity analysis as a percentage change to the technology transfer lead times. In 16 of 37 scenarios, the effect of parameter adjustment by +40 hr was found to be 0% on total lead time. Although this result was unexpected, after further review it was found that these parameters do not impact processes along the critical path of technology transfer and thus are not bottlenecks in the system. In addition, a few parameters were found to have slightly negative effects on technology transfer lead times. Although we do not expect the extension of a cycle time to lower the lead time, this phenomenon can be explained by normal variation in stochastic modeling.

The sensitivity analysis demonstrates that the model is not overly sensitive to individual process parameters, apart from parameter T_Data_Review. This parameter is called at the first

step in the model immediately following entity arrival and is on the critical path for technology transfer completion. Thus, it is expected that an adjustment of this parameter would amplify impact on lead times due to formation of queues at the very start of the process.

Parameter	Lead Time Effect	Parameter (continued)	Lead Time Effect (continued)
T_BBTA	1%	T_PEL_Plan	0%
T_BOM_D	4%	T_PEL_Results	0%
T_Buffer_Stability	5%	T_PEL_Run	0%
T_Comm_Protocols	0%	T_PPK	-1%
T_Data_Review	7%	T_PPQ_Tool	-1%
T_DS_Uniformity	0%	T_PPSR	1%
T_ELN_Entry	2%	T_PQRA	0%
T_Filter_Reten	-1%	T_PRD_D	0%
T_Gap_Analysis_D	-1%	T_PRD_Rev	0%
T_Gap_Analysis_Rev	-1%	T_Prefilt_MH	0%
T_IPCS	1%	T_PTD_D	1%
T_Mass_Bal_D	4%	T_PTD_Rev	0%
T_MBR_Rel	4%	T_RMRA	0%
T_Mfg_Assmnt	0%	T_SOP_Rel	2%
T_MMP	0%	T_SP_Requests	0%
T_NR_SP_D	2%	T_SS_Priortization	1%
T_PC_Prot	1%	T_Transcribe_Bom	0%
T_PC_Summ_Rpt	3%	T_V_Dataset	0%
T_PDSR	1%	-	-

Table 3-1: *Results of sensitivity analysis on model parameters. Parameters are listed in alphabetical order and split into two columns to fit on single page*

Chapter 4 Data Analysis

4.1 Business Process Visualization

The business process management software, Promapp, was used to visualize and communicate information regarding the technology transfer workflow. Translation of process requirements into Promapp was a critical step in the evaluation of Amgen's commercial technology transfer process for Drug Substance Process Development, as it provided a platform to apply lean principles for workflow improvement. Specifically, Promapp aided in the identification of procedure gaps, definition of roles and responsibilities, and training current and future technology transfer teams on a unified process.

The procedures recorded were organized by technology transfer phase. Within each phase contained a set of sequential activities and sub-procedures, structured in a hierarchical manner for simple extraction and communication. Each process activity contained task level details and linked to documents, SOPs, or web addresses where required. Also contained in each activity were future recommendations for process improvement identified through workflow mapping. Records of process changes were tracked using Promapp's change management feature to ensure traceability through the process evolution. Lastly, IT systems used to support technology transfer were defined within process steps in a manner which allowed reporting on system utilization. For confidentiality, the detailed set of process maps are not included in this research report. However, high level process flows for each phase within technology transfer can be found in Figures 4-1 to 4-3.

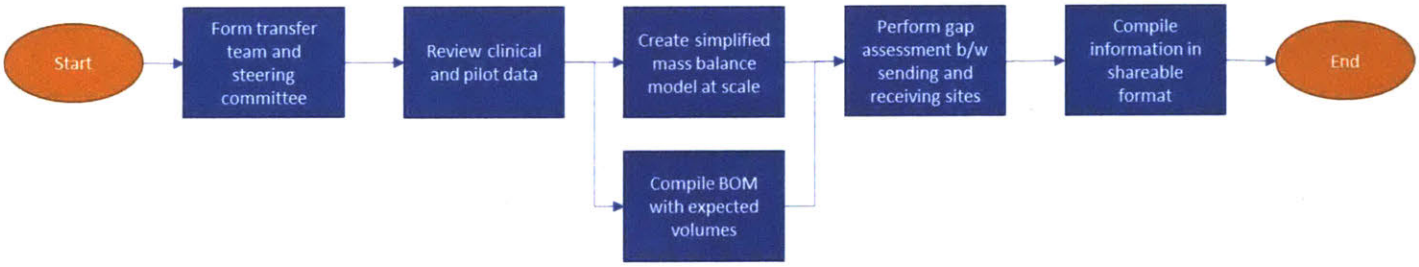

Figure 4-1: *High Level Process Map of Knowledge Transfer*

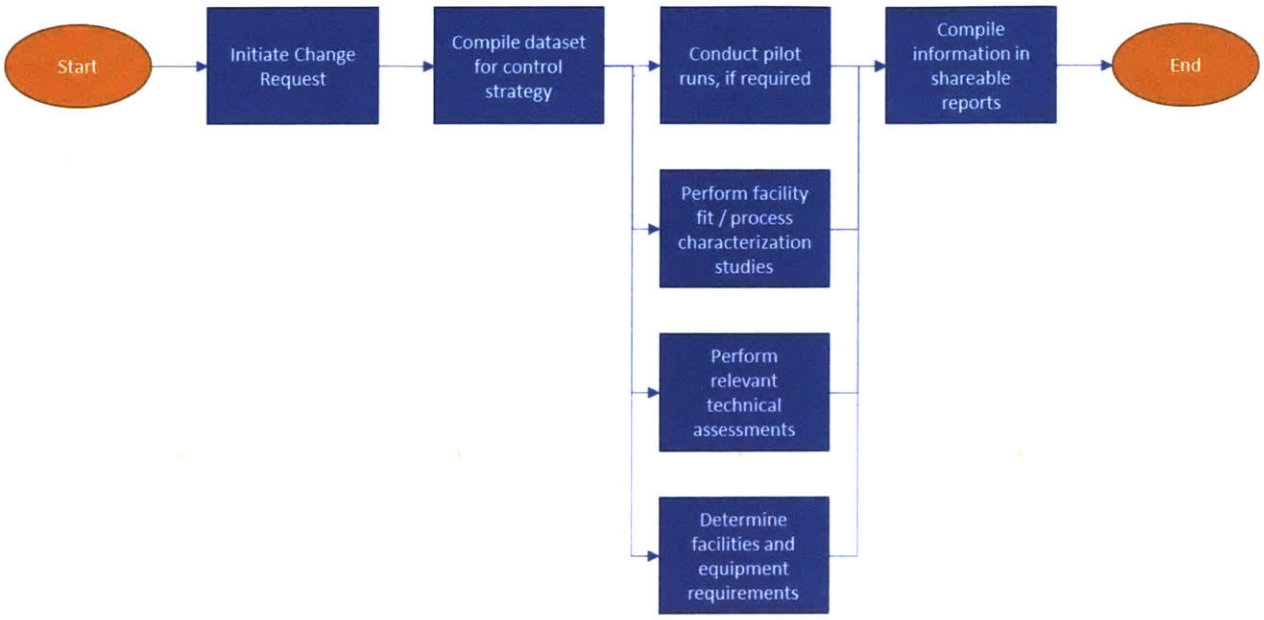

Figure 4-2: *High Level Process Map of Detailed Design*

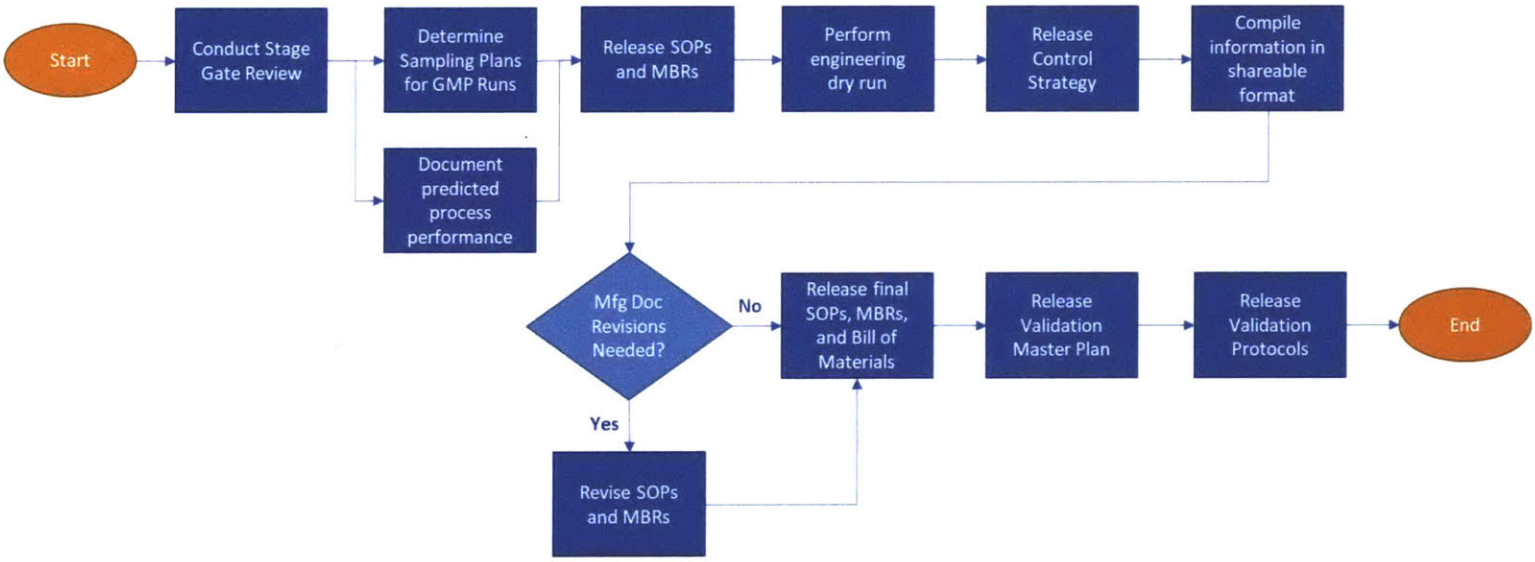

Figure 4-3: *High Level Process Map of PPQ Readiness*

To promote a collaborative environment for documenting and refining business processes, subject matter experts in technology transfer activities were provided access to use Promapp. Over four months, roughly 70 users were added to the system. In addition, the scope of process management expanded to contain technology transfer for Drug Product, technology transfer for contract manufacturing, Drug Substance Technology laboratory workflows, New Product

Introduction/Product Re-introduction, and Amgen academic interfaces. This scope expansion reflected Amgen's commitment to business process improvement.

4.2 Simulation Output and Verification

After the process steps were reviewed and agreed upon by members within Drug Substance Process Development, the base simulation was completed. The model was run to simulate 250 technology transfers, arriving consecutively at a normally distributed rate so that multiple technology transfer programs (WIP) may exist concurrently in the system. This number was chosen to collect a large sample of simulated outputs to fit distributions around main KPIs while accounting for computational limitations. The model defined a set number of Drug Substance Process Development technology transfer teams allotted for transfer support. At each program arrival, a technology transfer team was assigned to the program in a cyclical fashion.

The simulation was configured to model technology transfers assuming no major capital expenditure / construction required, 0 pilot runs required, and 1 engineering campaign before process validation. Outputs of the simulation with respect to technology transfer lead times from site selection to the start of Process Performance Qualification are displayed in a histogram in Figure 4-4. The lead time most closely follows a log-logistic distribution with min = 0, $\rho = 22.7$, and $\beta = 0.762$.

Capacity utilization for process development resources is listed in Table 4-1. Although utilization for select resources may seem low, it is important to note that the simulation only models resource utilization within the scope of technology transfer. Thus, work-related responsibilities which fall outside of the model boundaries are not accounted for in this calculation. Lastly, the total number of drug substance process development resources required to support transfer activities is depicted in figure 4-5, averaging a reasonable number of required PD resources per week supporting technology transfer activities, excluding ramp up and ramp down periods. Out of the utilized resources, roughly half are specific to the Drug Substance Technology and Engineering group.

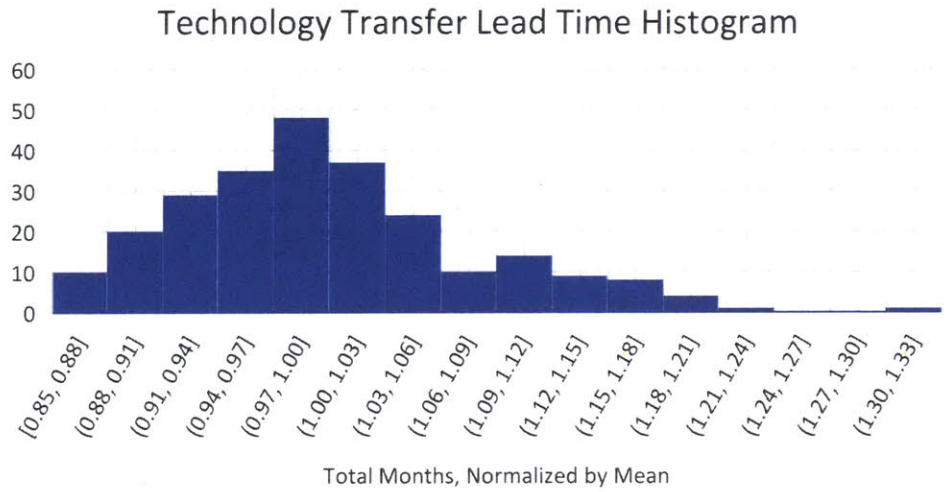

Figure 4-4: *Normalized Distribution of Simulated Technology Transfer Lead Times*

Role	TT US Leads	TT DS Leads	DST Scientist	Pivotal Lead US	Pivotal Lead DS	Receiving TTL	DSTL
Capacity Utilization	72%	69%	80%	61%	68%	20%	21%

Table 4-1*: Capacity Utilization of Technology Transfer Resources. (TT=Technology Transfer, US = Upstream, DS=Downstream, TTL = Technology Transfer Lead, DSTL = Drug Substance Technology Lead, and DST = Drug Substance Technology)*

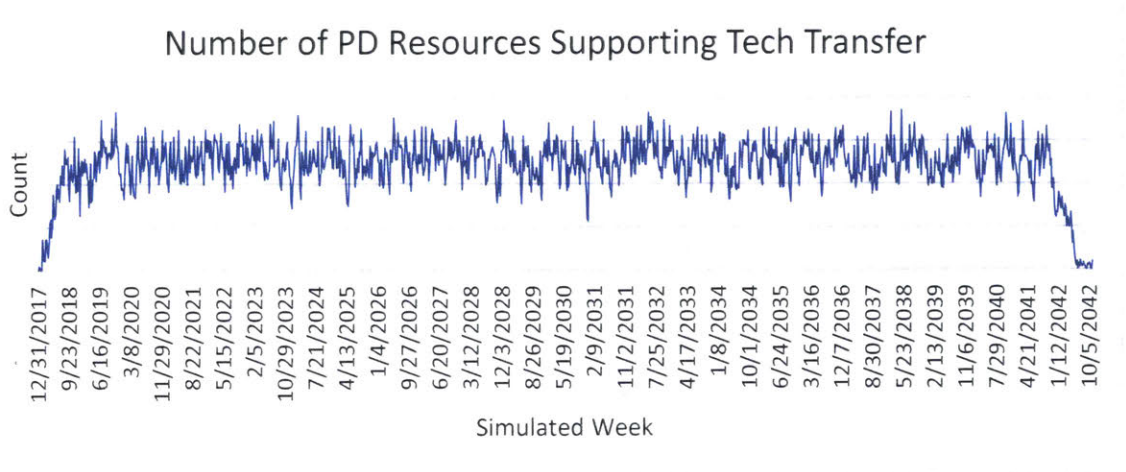

Figure 4-5: *Average number of DSTE Resources utilized per week over simulated timeframe. Note: FTE count on y-axis is redacted for confidentiality*

4.3 Simulation Output Verification

The model output with respect to process cycle time was compared against empirical data from the chosen architype. Model accuracy was calculated using

$$Accuracy = 1 - \frac{|CT_s - CT_e|}{CT_e}$$

***Equation 4-1**: Cycle Time accuracy of simulation model, where e = empirical and s = simulated*

As seen in Table 4-2, the simulation output fell within 70-100% accuracy for modeled process steps, averaging an accuracy of 88%. Given the nature of the business process modeled and the human behavior, prioritization, and decision-making which affect KPIs measured, this is considered a reasonable margin to proceed with scenario analyses for process improvements.

Knowledge Transfer Steps	Accuracy	Detailed Design Steps	Accuracy	PPQ Readiness Steps	Accuracy
Data Package Review	88%	Buffer Stability Assessment	87%	Engineering BOM	99%
Mass Balance	98%	PC Prioritization	70%	SOP + MBR Release	76%
Bill of Materials	95%	PC Summary Reports	100%	Engineering Run	99%
Gap Identification	91%	Process Parameters Rpt	93%	Final SOP Release	90%
Requirements Definition	82%	Process Design Rpt	73%	Final MBR Release	89%
PTD, V1 Release	76%	Process Instrument List	97%	Final BOM Release	95%
Gap Analysis and Mitigation	91%	Raw Material Specs	84%	Final PTD Release	95%
Mfg. Assessment	82%	Functional Specs	89%	Validation Protocols	78%

***Table 4-2:** Simulation Output Accuracy*

4.4 System Bottlenecks and Critical Path

The simulation model results were used to identify critical path(s) within the technology transfer business process. Through analyzing the model outputs, including start and stop time stamps for each simulated process activity, two parallel paths were identified as critical to the end to end lead time for commercial technology transfer. The first critical path is regarding completion of facility fit studies in support of process characterization. This activity is required to release the final process parameters and manufacturing process design, which are needed to produce

automation code, manufacturing SOPs and batch records. The second critical path surrounds site readiness activities at the receiving facility. The two critical paths diverge after the site capabilities gap analysis and converge at the release of the final process transfer document (PTD). These critical paths align with management intuition, supporting the model's reflection of observed behavior (see Figures 4-6 and 4-7 for a screenshot of the critical paths taken from Promapp). Figure 4-8 depicts the elements shared between the two critical paths before they split and after they converge.

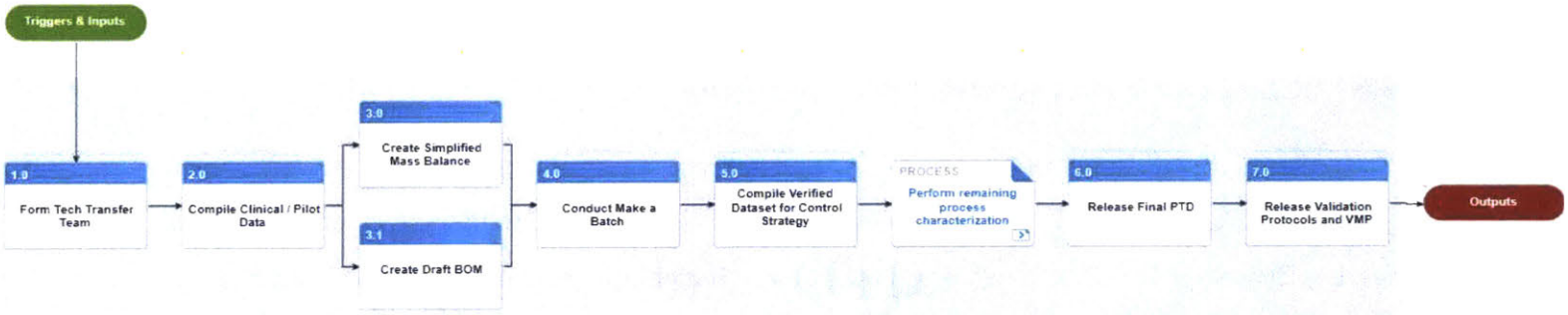

Figure 4-6: *Process Characterization Critical Path*

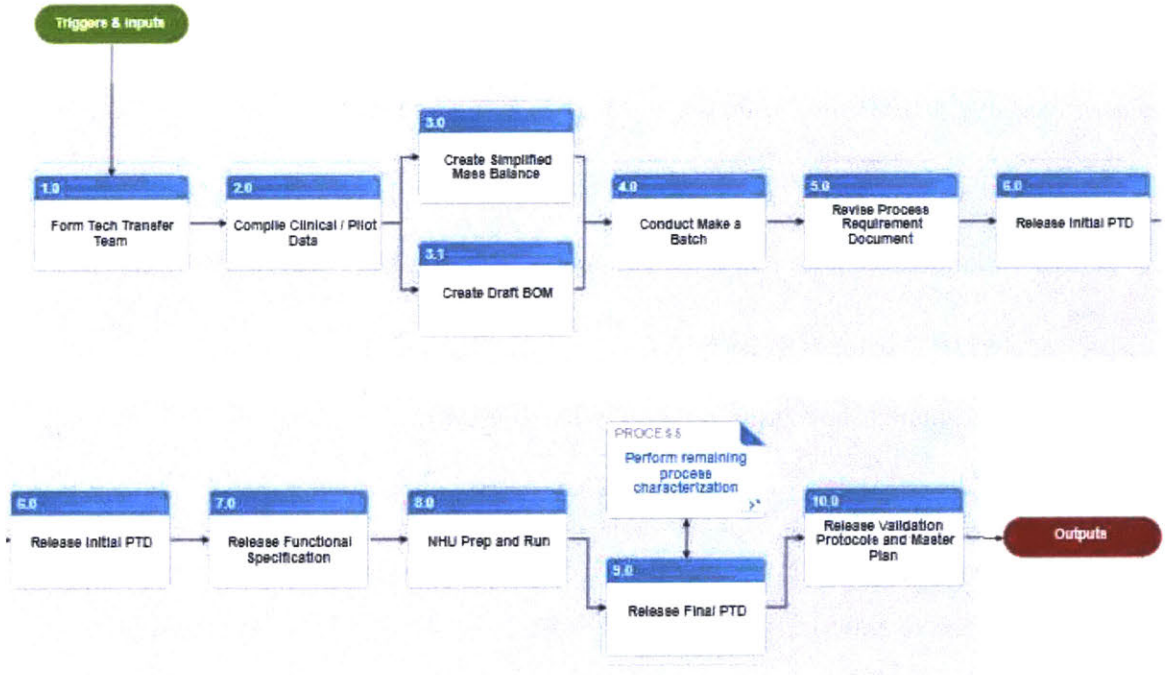

Figure 4-7: *Site Readiness Critical Path, split to allow for legibility on page*

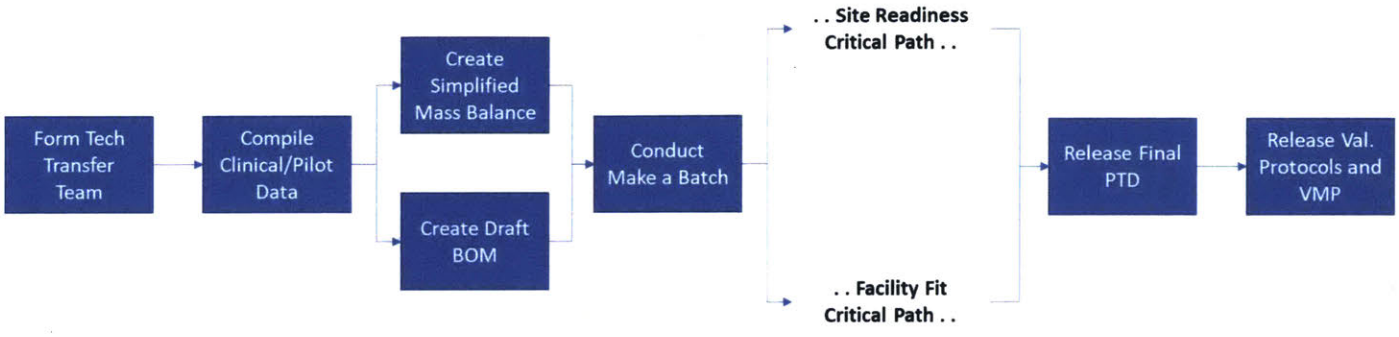

***Figure 4-8**: A depiction of the common elements shared between the two critical paths*

4.5 SCENARIO ANALYSIS FOR PROPOSED SOLUTIONS

Upon identification of the two critical paths, a workshop was conducted with a cross functional team involved in technology transfer activities. Similar to the value stream mapping session discussed in Chapter 3.2 of this document, functions present in the workshop included Drug Substance Technologies and Engineering, Pivotal Drug Substance, Facilities and Equipment Project Management, Manufacturing Engineering, and Validation. The purpose of the workshop was to identify process improvement opportunities which target workstreams impacting the critical paths, resulting in reduced technology transfer lead times. Process improvement ideas discussed and approved by the workshop team for further modeling and analysis are

1. Alignment of best practices across technology transfer programs
2. Pool upstream and downstream technology transfer resources within DSTE
3. Improve process sequencing
4. Automate information transfer, where possible
5. Create standard report templates for critical technology transfer deliverables

The results were summarized in an effort vs. impact four-box as shown in Figure 4-9. Additional details regarding these proposals are included in Sections 4.5.1-4.5.3 of this document.

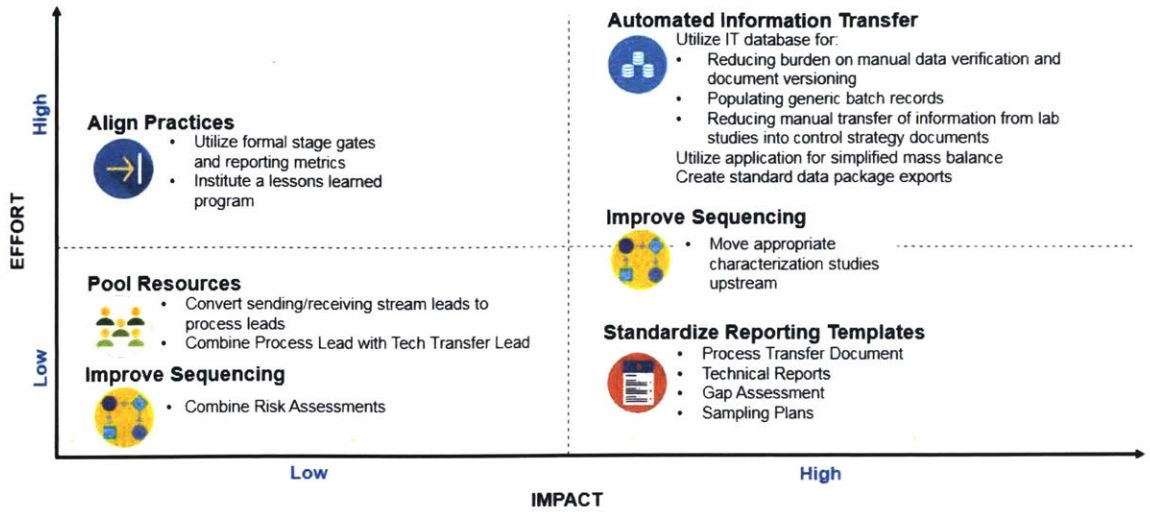

Figure 4-9: *A summary of proposed process improvements*

4.5.1 Lean Tools for Process Standardization

The workshop team identified a lack of standardization within technology transfer, resulting in mixed understanding and rework on required deliverables. To address this issue, lean thinking was used to recognize sources of waste within the technology transfer process and identify methods to increase comprehension of required tasks and enhance visibility to team responsibilities. Standard templates were proposed for major technology transfer deliverables, including the process transfer document and gap assessments. Such templating would allow for a clear depiction of required deliverable content, thus eliminating confusion between teams and over-processing of tasks. Redundancies in gap assessments were also found, highlighting opportunities to streamline and further control via proposed templating. In addition, the team agreed that implementation of formal stage gates and alignment of process metrics may improve communication and process understanding across programs.

The workshop team also identified opportunities to pool resources within Drug Substance Process Development to smooth variability in capacity utilization. Specifically, a proposal was made to combine upstream and downstream technology transfer leads into general lead roles that can delegate tasks to process scientists as needed. During this assessment of resources responsibilities, an opportunity to reduce the number of technology transfer program leads from two to one was identified. This proposal was made to eliminate redundancy in responsibilities as well as allow a single point of contact for technology transfer decision points.

Lastly, the workshop team noted a lack of communication across technology transfers and a need for project teams to share best practices. Thus, a proposal to institute a lessons-learned program was made. As proposed, the program would contain not only obstacles observed during transfers, but an assessment of their impact and traceability to implemented solutions. In addition, the lessons-learned program would be easily searchable and accessible to all personnel involved in technology transfer.

4.5.2 Platform Process Characterization

As process characterization for commercial facility fit is along the critical path, leadership from the Drug Substance Pivotal organization reviewed standard facility fit activities to identify improvement mechanisms. Leadership identified an opportunity to move two specific process characterization studies upstream in the technology transfer workflow, before the completion of the site capabilities gap analysis and outside the scope of facility fit. This idea was considered feasible as insights from the gap analysis do not directly feed requirements for the studies in question, and thus the sequential dependency is not required. The resulting impact of this change would be a reduction in facility fit studies along the critical path by 50%. Furthermore, it would reduce the number of process characterization summary reports by 22%. Thus, this change provides ample information to assess total impact on technology transfer timelines using a modified simulation model.

4.5.3 Automated Workflows and Information Systems

Capabilities for automated workflows and information systems to aid in data storage and transmission were reviewed. Through this assessment, the workshop team discussed opportunities to streamline the flow of information from laboratory studies to process parameter and process design documents, thus reducing manual data mining and verification. Similarly, the team also noted an opportunity to transmit information from control strategy documents into critical deliverables for process transfer including batch records and the Process Transfer Document, further reducing manual data translation. Lastly, the workshop team explored an opportunity to use stored information on site requirements and capabilities to aid in the creation of a simplified mass balance model during knowledge transfer.

4.5.4 Assumptions for Scenario Analysis

We assessed the process improvement opportunities for their ability to be modeled in the discrete event simulation. As the proposals lacked data and information, select ideas could not be quantified for the purposes of performing a scenario analysis. For example, the effects of instilling a lessons-learned program and project stage gates on cycle times and resource utilization are unknown, and thus could not be accurately modeled. However, such ideas are certainly important to promoting standardization, and thus remain in scope of our recommendations.

We identified 10 process changes as feasible for scenario analysis. The process changes are broken into low- to medium-effort opportunities with minimal infrastructure required, and high-effort opportunities requiring capital expenditure and process transformation for automated information systems. The improvement mechanisms and respective assumptions are listed in Table 4-3. It is important to note that the assumptions used are conservative estimates to demonstrate the minimum potential gain from process improvements. Each process change was built into Promodel's scenario analysis for assessment. Results of analysis are discussed in Chapter 5.

Item	Effort	Process Change	Model Assumptions
1	Low	Convert Sending/Receiving Stream Leads to Process Leads	Former upstream and downstream leads share technology transfer responsibilities between streams
2	Low	Combine Process Lead with Technology Transfer Lead	Assign a senior receiving lead the responsibilities of technology transfer lead
3	Low	Combine manufacturability assessment with site capabilities gap analysis	Manufacturability assessment is no longer required - remove step from simulation
4	Medium	Move two characterization studies upstream	Reduce total number of upstream facility fit study blocks by 50%. Reduce number of required process characterization summary reports along critical path by 22%.
5	Low	Standardize Reporting Templates	Estimated time required to draft and release select reports can reduce by 25%.
6	High	Reduce burden of manual data mining and verification on process transfer document	Estimated time required to draft select reports can reduce by another 25%. Data verification step can be removed.
7	High	Reduce manual data translation from laboratory studies into control strategy	Estimated time required to draft control strategy reports can reduce by 25%. Data verification step can be removed.
8	High	Populate generic batch records from electronic database	Estimated time required to draft batch records can reduce by 25%. Time to release in document control system can be eliminated
9	High	Automate simplified mass balance	Estimated Time required to develop simplified mass balance model can be reduced by 25%. Time to route for review and can be eliminated.
10	High	Create standard data packages	Estimated time required to develop data packages can be reduced by 90%. Data verification step can be removed.

Table 4-3: *A list of process changes and associated assumptions for scenario analysis*

Chapter 5 Results and Discussion

5.1 Scenario Analysis Results

The model was run to test each improvement opportunity individually to determine singular impact of process changes with respect to technology transfer lead times. Due to the nonlinearity of the technology transfer process and the need for activities to run in parallel, significant benefits were not observed when one improvement mechanism was implemented at a time. However, when process changes were combined, the overall impact on technology transfer lead time was improved. Table 5-1 outlines percent improvements to mean lead times for the following scenarios, keyed to the respective item number(s) in Table 4-3:

1. Scenario 1: Baseline simulation. No process changes
2. Scenario 2: Combine selected assessment into site capabilities gap analysis (3)
3. Scenario 3: Implement platform facility fit studies for tests independent of receiving site (4)
4. Scenario 4: Create standard data packages for select data exports (10)
5. Scenario 5: Implement standard templates for Process Development deliverables (5)
6. Scenario 6: Automate simplified mass balance using database on site capabilities (9)
7. Scenario 7: Automate data transfers for deliverables requiring manual data verification (6, 7, 8)
8. Scenario 8: Pool upstream and downstream DSTE resources and technology transfer lead (1, 2)

Scenario	1	2	3	4	5	6	7	8	Combined Low-Med Impact: Scenarios 3, 5, 8	Combined Low-High Impact: Scenarios 3 - 8
% improvement	N/A	0.00%	5.11%	1.04%	3.01%	1.81%	4.41%	2.83%	10.49%	19.50%

Table 5-1: *Lead Time Improvements by Scenario. As Scenario 2 provided no improvement in lead time, it was not further analyzed in combined scenarios*

5.2 SIMULATION INSIGHTS

5.2.1 Improvements in Lead Times and Process Variability

The results of the scenario analysis demonstrate that with a low degree of effort and minimum changes to supporting infrastructure, reductions in technology transfer lead times can be observed. As the assumptions made in the process modeling were conservative estimates, we assume that low-medium effort changes can result in a minimum of 10.5% improvement gain in technology transfer lead times. This number improves to 19.5% reduction in technology transfer with the implementation of automated workflows and information systems. Table 5-2 compares the mean, standard deviation, and 80th percentile lead time between the baseline scenario, low-medium effort improvements (Scenarios 3, 5 and 8 from Table 5-1), and low-high effort improvements (Scenarios 3-8 from Table 5-1). These mean and variance of lead times is also visualized in Figure 5-1.

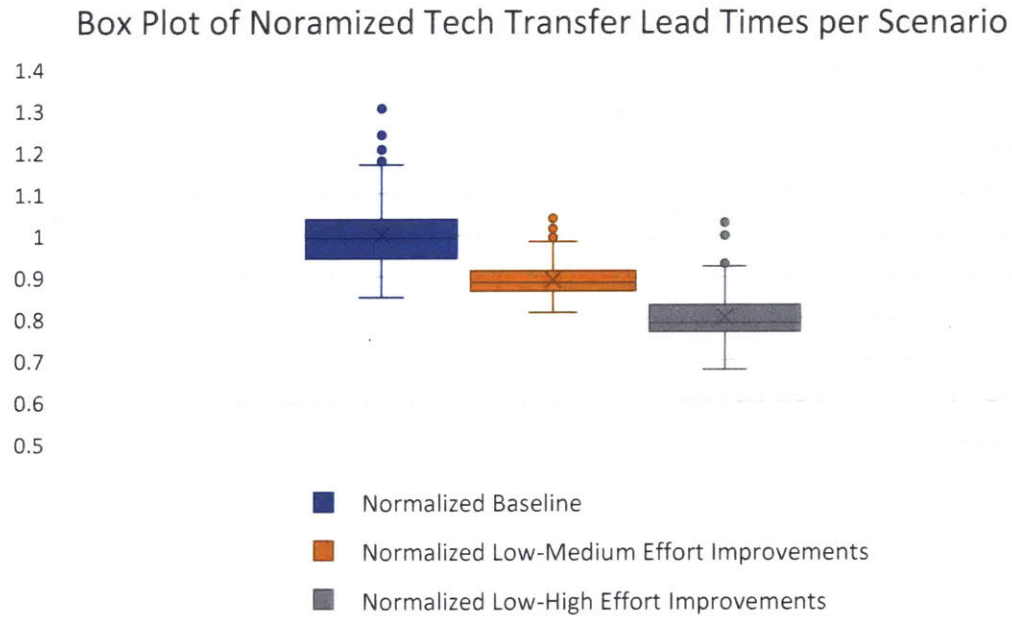

Figure 5-1: *Box Plot of technology transfer lead times per scenario, normalized over baseline mean*

Metric / Scenario	Baseline	Low-Medium Effort Improvements	Low - High Effort Improvements
Normalized Mean	1.000	0.892	0.803
Standard Deviation	1.025	0.498	0.723
Normalized 80th Percentile	106%	93%	84%

Table 5-2: *Comparison of lead times across three scenarios tested, normalized over baseline mean*

5.2.2 Capacity Management

In both low- and high-effort improvement scenarios, the number of PD resources assigned to technology transfer activities was reduced by 20% due to resource pooling and combining of leads. In addition, the capacity utilization per resource reduced, due to streamlined workflows and waste elimination. The capacity utilization per resource is depicted in Table 5-3.

Role	TT US Leads	TT DS Leads	DST Scientist	Pivotal Lead US	Pivotal Lead DS	Tech Transfer Lead	DSTL
Baseline Utilization	72%	69%	80%	61%	68%	20%	21%
Role	**TT RS Lead**	**TT SS Lead**	**DST Scientist**	**Pivotal Lead US**	**Pivotal Lead DS**	**Tech Transfer Lead**	**DSTL**
Low-Medium Effort Improvement Utilization	60%	57%	63%	58%	62%	0% (Combined with Receiving Lead)	21%
Low - High Effort Improvement Utilization	62%	55%	64%	58%	59%	0% (Combined with Receiving Lead)	22%

Table 5-3: *Comparison of resource capacity utilization by scenario*

Given the change in capacity utilization per resource, we identified an opportunity to explore the impact of reducing the number of process development teams dedicated to technology transfer activities. Thus, within the simulation model, we decreased the number of total teams available to take on incoming transfers by 25%. This in turn resulted in a greater overlap of programs that designated resources were responsible for at any given time. The results depicted in Table 5-4 and Figure 5-2 demonstrate that with modeled process improvements, process

development can reduce the total number of FTEs assigned to technology transfer activities by 31.3% (through team reduction and resource pooling) without significantly impacting technology transfer lead times. However, an increase in lead time variability is observed.

The insights gained from the reported scenarios are noteworthy and demonstrate the potential to increase FTE efficiency significantly with modeled process changes. The results can help to inform management on program impact from capacity management decisions. With the simulation results, the organization can determine whether to assign more process development teams to technology transfer activities to increase probability of achieving KPIs on critical programs, or to allocate resources to other initiatives within the organization.

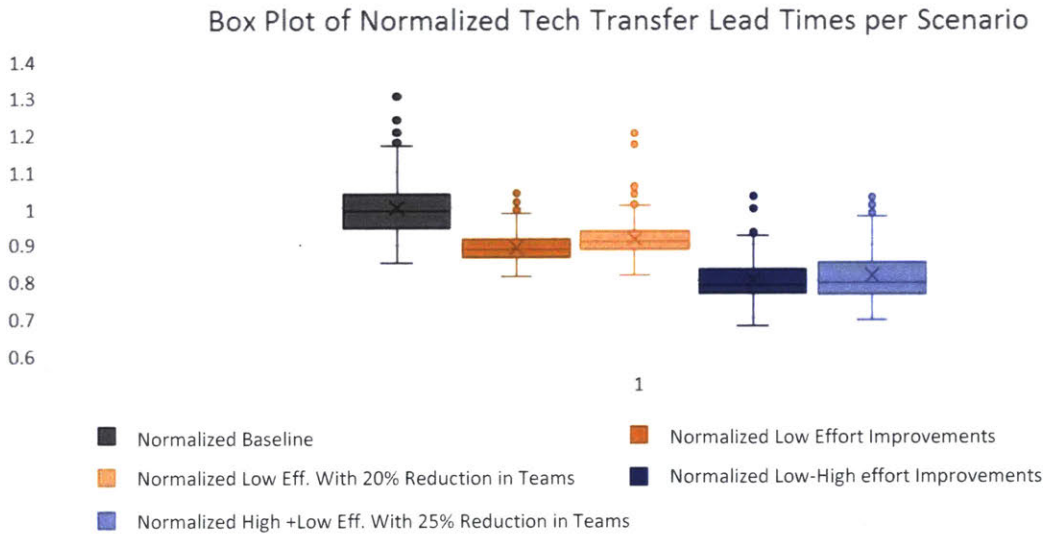

Figure 5-2: *A comparison of technology transfer lead times across capacity management scenarios, normalized over baseline mean.*

Role	TT RS Lead	TT SS Lead	DST Scientist	Pivotal Lead US	Pivotal Lead DS	Tech Transfer Lead	DSTL
Low-Med Effort Improvement Utilization	60%	57%	63%	58%	62%	0% (Combined with Receiving Lead)	21%
Low-Med eff. + 25% Team Reduction	76%	69%	75%	67%	75%	0% (Combined with Receiving Lead)	28%
Low-High Effort Improvement Utilization	62%	55%	64%	58%	59%	0% (Combined with Receiving Lead)	22%
Low-High Eff. + 25% Team Reduction	75%	68%	76%	69%	73%	0% (Combined with Receiving Lead)	27%

Table 5-4: *a comparison of capacity utilization across improvement scenarios with 25% reduction in total number of process development teams assigned to technology transfer activities*

5.3 Bayesian Analysis of Simulation for Project Scheduling

Through this work, we have demonstrated the ability to use discrete event simulation to characterize the complex dynamics of a business process, thereby providing insights into process improvement mechanisms and allowing us to measure their effectiveness against capacity utilization and lead times. In addition to a process improvement utility, we have also uncovered the opportunity to use discrete event simulation for project forecasting and real-time program management. Specifically, information regarding project lead times and capacity management can be assessed along stage gates for a business process, given information known on a project's status. This Bayesian assessment can provide teams with real-time probabilities of achieving their KPIs and allow for adjustments to project schedule or resource allocation as needed.

Let us take, for example, a program scheduled to complete commercial technology transfer to an internal manufacturing facility. At the start of the program, the project team may foresee that capital expenditure is required for new equipment to support manufacturing of alleged product, as well two independent studies to test processing at a pilot scale. The project team may expect a standard number of gaps identified during the gap assessment given the modality of the

molecule and commercial site capabilities. Lastly, the team may estimate a select number of facility fit studies required to support the process control strategy.

Based on the information known initially, a discrete event simulation can be run to simulate a reasonable number of programs with defined parameters to obtain a probability distribution of lead times. An example of such distribution of shown in Figure 5-3. Project management can use the insights gained from the simulation to create a feasible project schedule and build a team of personnel to support transfer activities. A project manager may, for example, set a project schedule based on the 80th percentile of lead times for simulated programs. As there is no data available yet on actual completion times and resource requirements, the variability in simulation output is presumed large. However, as more information is gained, stochasticity in model variables will decrease, resulting in narrowed window of model output.

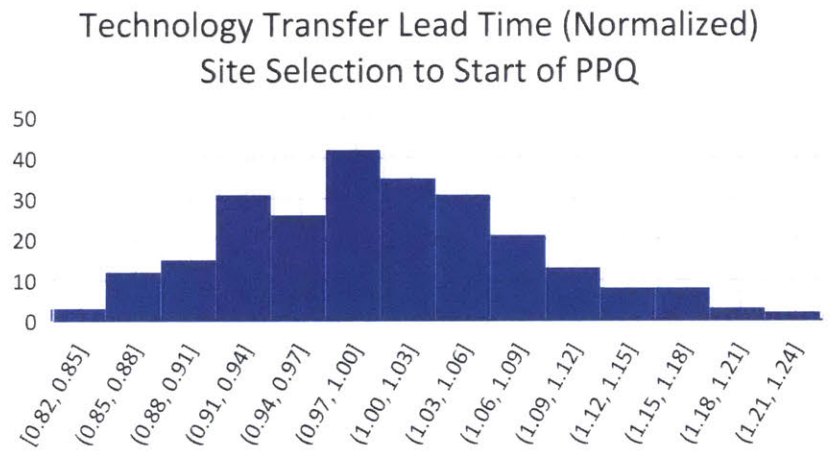

Figure 5-3: *Normalized histogram of predicted technology transfer lead times at the beginning of a program*

Now let us assume that the project has reached its halfway point, with the gap assessment, facility fit studies, and equipment construction completed. The simulation scope has been reduced to only include tasks left to be performed. If the project is at a formal stage gate, the results of the simulation can be added to the observed project duration to determine the newly predicted lead time, given the program status. Assuming the project has progressed per original schedule, the predicted mean lead time remains the same, but variability decreases. Thus, the probability that the program is completed within the targeted 80th percentile given program status increases.

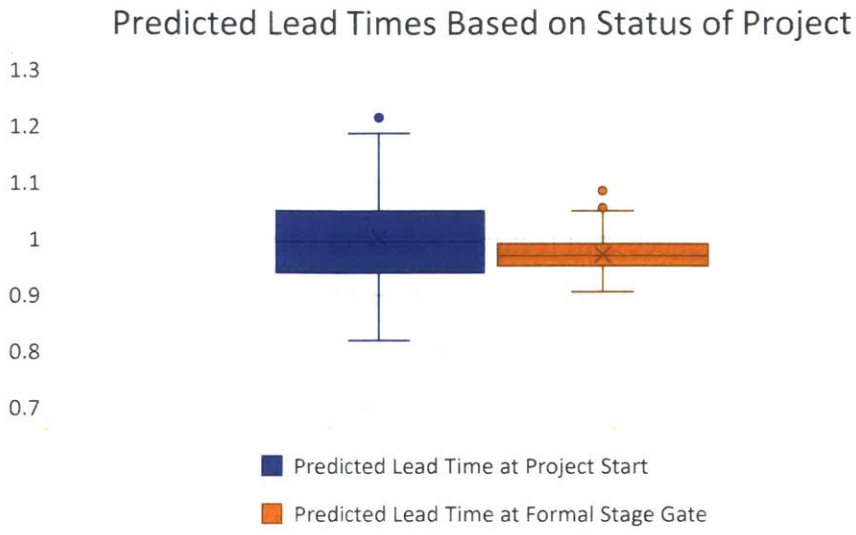

Figure 5-4: *Simulated lead times given project actuals, based on sample case*

This case demonstrates the ability to use discrete event simulation for real time assessment of a program's progress against set KPIs. However, changes to program management practices are required before implementing this technique in practice. Primarily, the organization must design formal stage gates where pre and post activities are cleanly separated. By disentangling project steps through formal stage gates, project management can easily predict real-time adherence to KPIs with knowledge of current project duration and data on future task simulations. Without this project management structure, significant modifications to the model use would be required to ensure an accurate representation of total project lead time and capacity utilization. However, if properly implemented, a Bayesian analysis to project management would aid in improved adherence to project schedules as well as an enhanced understanding across project teams on program dynamics and dependencies.

Chapter 6 Conclusion and Recommendations

6.1 General Findings and Impact on Process Development at Amgen

Biopharmaceutical technology transfer is a complex business process involving personnel across functions and sites. A successful technology transfer requires keen project management to maintain balances between capacity utilization, cost, and project throughput. The work discussed in this document explored the intricacies of conducting and managing commercial technology transfers. A deep assessment was performed on required tasks, deliverables, and dependencies within the technology transfer business process. In addition, capacity utilization of technology transfer teams was assessed to determine levels of adequate staffing and resources needed to support an enterprise's pipeline.

As many workstreams must run in parallel during technology transfer, multiple critical paths exist which impact technology transfer lead times. For this reason, there is no "smoking gun" technique to make a significant impact on resource utilization and project lead times. Rather, we found that a combination of modest, incremental improvements to process steps lead to measurable changes. Specifically, with reasonable assumptions, we demonstrated that applying Lean Thinking to the technology transfer business process through implementation of standard templates, resource pooling, and adjustments to process sequencing had the potential to reduce lead times by a minimum of 10.5% and improve resource efficiency by 31.3%. Moreover, lead time improvements can be further increased to 19.5% through implementation of automated workflows to aid in information transfer. However, we understand that such change would require large capital investment, process transformation, and employee training to be successful.

Not modeled in this work is the impact of "Technology Transfer by Design" principles to control the active management of projects and improve communication and reporting channels. Enforcing standard stage gates for project management and standardizing metrics across programs would support these principles and promote consistency across programs and project teams. Furthermore, implementing a lessons-learned program that can be shared across members involved in technology transfer would aid in promoting knowledge sharing and continuous improvement on a global scale. Although these improvement techniques could not be modeled, we believe that they would significantly impact how technology transfers are conducted over time.

Also explored in this work was the possibility to utilize discrete event simulation for real-time program management. We showed that, with small adjustments, the simulation model can be used in a Bayesian fashion to report program projections, given information known on the activities completed. This technique is an improvement over static project scheduling approaches as it considers capacity management and the inherent stochasticity within task completion, thus providing a more relevant assessment of a project's status. Furthermore, a simulation model can better inform project management of scheduling risks and forthcoming resource needs to ensure a project's success.

6.2 Assessment of Solutions against Cost to Enterprise

As we assessed the potential improvement opportunities within technology transfer, we rated each opportunity against implementation effort and improvement impact. Low-medium effort techniques which would provide a significant impact on technology transfer KPIs include moving towards platform studies for specific process characterization studies which are independent of commercial site selection. Amgen's Pivotal Drug Substance Technologies group has proven the feasibility of this change and is vested in its implementation. In addition, creation of standard templates is a low-effort change requiring little capital expenditure, yet has the potential to improve lead times, process understanding, and consistency. We have begun assessing requirements for templating a critical technology transfer report for Drug Substance Technologies and Engineering. However, to successfully implement this work, the organization must manage both the resources and buy-in required to release and use the standard templates moving forward.

We found that resource pooling across upstream and downstream functions within Drug Substance Technologies and Engineering had the potential to reduce variability in capacity utilization. This in turn decreased lead times by reducing the number of work in process queued. However, we would like to proceed with caution in this recommendation, as we respect the importance of maintaining expertise in the scientific disciplines supporting upstream and downstream process development. Thus, we only recommend pooling of resources for stream leads, and propose that Amgen maintains stream dependencies for process characterization and commercial process development.

Lastly, we found that implementation of automated workflows and information systems to support data transfer had the highest impact on process lead times. Specifically, automated data transfers on critical path items including the process control strategy, the process transfer document, and batch record templates reduced technology transfer lead times by a minimum of 9.5%. However, this is also the most resource intensive process improvement that requires a capital budget and scheduled time to define user requirements, develop the infrastructure, and train personnel on newly developed systems. For that reason, this change must be endorsed by executive management and cannot be implemented immediately.

6.3 PROPOSALS FOR FUTURE WORK

6.3.1 Realization of Benefits from Expansion of Scope

This work was focused on optimizing Amgen's commercial technology transfer processes for Drug Substance Process Development. We carefully scoped our work to include an assessment of technology transfer activities from commercial site selection to the start of process performance qualification. Through this research, we showed the feasibility of using discrete event simulation and business process management techniques to characterize a business process and gain insights into feasible changes for process optimization.

As we look ahead, we perceive opportunities to utilize the methodology established in this research project to advance practices across Amgen's Technology Transfer Global Network. Specifically, discrete event simulation and business process management can support the characterization and improvement of commercial technology transfers for drug product, final drug product, and attribute sciences. These future assessments require champions across Amgen, from senior management to the scientists and engineers who regulatory operate within the systems analyzed. However, with a unified effort, we believe that discrete event simulation and business process management can assist Amgen in unlocking optimization opportunities on a global scale. Above all, these techniques can stimulate changes which improve organizational capacity and enhance process efficiency across Process Development. Such benefits are critical to the growth and development of Amgen's strategic pipeline.

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